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(54) Title: INTERLEUKIN-17 RELATED MAMMALIAN CYTOKINES. POLYNUCLEOTIDES ENCODING THEM. USES (54) Titre: CYTOKINES DE MAMMIFERES LIEES A L'INTERLEUKIN-17, POLYNUCLEOTIDES LES CODANT ET LEURS UTILISATIONS	
(57) Abstract CTLA-8 related antigens from mammals, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding said antigens. Methods of using said reagents and diagnostic kits are also provided. (57) Abrégé L'invention porte sur des antigènes de mammifères, apparentés à CTLA-8, sur des réactifs associés auxdits antigènes, sur des anticorps spécifiques et sur des acides nucléiques codant lesdits antigènes. Des procédés d'utilisation desdits réactifs et des trousse de diagnostic sont également décrits.	

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ing Hill Road, Kenilworth, NJ 07033-0530 (US).

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KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK,
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(54) Title: INTERLEUKIN-17 RELATED MAMMALIAN CYTOKINES. POLYNUCLEOTIDES ENCODING THEM. USES

(57) Abstract: CTLA-8 related antigens from mammals, reagents related thereto including purified proteins, specific antibodies, and nucleic acids encoding said antigens. Methods of using said reagents and diagnostic kits are also provided.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N15/24 C07K14/54 A61K38/20 C07K16/24 G01N33/68		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 C12N C07K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, STRAND, WPI Data, BIOSIS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 49310 A (ZYMOGENETICS INC) 5 November 1998 (1998-11-05) sequences ID no.1,2,11 and 12 page 40; example 1 --- -/-	1-20
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claims) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *Z* document member of the same patent family		
Date of the actual completion of the international search 27 July 2000		Date of mailing of the international search report 07.08.00
Name and mailing address of the ISA European Patent Office, P.B. 5618 Palantian 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tr. 31 651 epo nl. Fax: (+31-70) 340-3016		Authorized officer Le Cornec, N

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INTERNATIONAL SEARCH REPORT

 Int'l Application No
 PCT/US 00/00006

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	<p>A. SOTO-PRIOR ET AL: "Identification of preferentially expressed cochlear genes by systematic sequencing of a rat cochlea cDNA library"</p> <p>EMBL DATABASE ENTRY U74047, ACCESSION NUMBER U74047,</p> <p>5 September 1997 (1997-09-05), XP002138048</p> <p>"100% identity with sequence ID no.9 in 133 bp overlap"</p> <p>-& A. SOTO-PRIOR ET AL: "Identification of preferentially expressed cochlear genes by systematic sequencing of a rat cochlea cDNA library"</p> <p>BRAIN RESEARCH MOLECULAR BRAIN RESEARCH, vol. 47, no. 1-2, 1997, pages 1-10, XP000907220</p> <p>abstract</p> <p>---</p>	1-6,8
X	<p>M. BONALDO ET AL: "Human chromosome specific mRNA"</p> <p>EMBL DATABASE ENTRY HSN0TIA, ACCESSION NUMBER L23206,</p> <p>15 December 1993 (1993-12-15), XP002138049</p> <p>* 100% identity in 310 bp overlap with sequence ID no.5 reverse orientation and 99.3% identity in 323 bp overlap with sequence ID no.7 reverse orientation *</p> <p>abstract</p> <p>---</p>	1-6,8
X	<p>NCI-CGAP: "National cancer institute, cancer genome anatomy project (CGAP), tumor gene index"</p> <p>EMBL DATABASE ENTRY AI275406, ACCESSION NUMBER AI275406,</p> <p>23 November 1998 (1998-11-23), XP002138050</p> <p>abstract</p> <p>* 99.8% identity in 441 bp overlap with sequence ID no.5 *</p> <p>& UNPUBLISHED,</p> <p>---</p>	1-6,8
X	<p>M. MARRA ET AL: "The WashU-HHMI Mouse EST project"</p> <p>EMBL DATABASE ENTRY MM18637, ACCESSION NUMBER W88186,</p> <p>4 July 1996 (1996-07-04), XP002143640</p> <p>* 83% identity with sequence ID no.13 and 15 in 387 bp overlap and 100% identity in 418 bp overlap with sequence ID no.17 *</p> <p>abstract</p> <p>& UNPUBLISHED,</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-6,8

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/00006

C/(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	L. HILLIER ET AL: "The WashU-Merck EST project" EMBL DATABASE ENTRY HS04078, ACCESSION NUMBER R09040, 20 April 1995 (1995-04-20), XP002143641 * 97,6% identity in 379 nt overlap with seq ID no.29 * abstract & UNPUBLISHED,	1-6,8
X	L. HILLIER ET AL: "The WashU-Merck EST project" EMBL DATABASE ENTRY HS843253, ACCESSION NUMBER H93843, 5 December 1995 (1995-12-05), XP002143642 * 97,2% identity in 323 nt overlap with seq ID no.27 * abstract & UNPUBLISHED,	1-6,8
A	WO 97 04097 A (GENETICS INST) 6 February 1997 (1997-02-06) the whole document	1-20
A	YAO Z ET AL: "HUMAN IL-17: A NOVEL CYTOKINE DERIVED FROM T CELLS" JOURNAL OF IMMUNOLOGY,US,THE WILLIAMS AND WILKINS CO. BALTIMORE, vol. 155, no. 12, 15 December 1995 (1995-12-15), pages 5483-5486, XP000602481 ISSN: 0022-1767 cited in the application the whole document	1-20
A	WO 95 18826 A (SCHERING CORP ;INST NAT SANTE RECH MED (FR)) 13 July 1995 (1995-07-13) Sequence ID no.7 and no.8 claims	1-20
P,X	WO 99 61617 A (HUMAN GENOME SCIENCES INC ;EBNER REINHARD (US); RUBEN STEVEN M (US)) 2 December 1999 (1999-12-02) sequences ID no. 28, 29, 31 and 32 claims; figures 6,8 examples	1-20
E	WO 00 15798 A (ZYMOGENETICS INC) 23 March 2000 (2000-03-23) especially sequences ID no.1,2,5,8 and 9 the whole document	1
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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/US 00/00006

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 60127 A (CHEN JIAN ; GENENTECH INC (US); LI HANZHONG (US); FILVAROFF ELLEN () 25 November 1999 (1999-11-25) Sequence ID no.3 claims; figure 3 -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/00006

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 00 00006

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1a, 2a, 3a , 5a, 9a, 11A, 14a, 15a and (4, 6, 7, 8, 10, 12, 13, 16, 17, 18, 19, 20) partially

Mammalian iL-173. Polynucleotides represented by sequences ID no.5,7,9 and 11 and polypeptides represented by sequences ID no.6,8,10 and 12. Antibodies. Uses thereof.

2. Claims: 1b, 2b, 3b , 5b, 9b, 11B, 14b, 15b and (4, 6, 7, 8, 10, 12, 13,16, 17, 18, 19, 20) partially

Mammalian iL-174. Polynucleotides represented by sequences ID no.13,15 and 17 and polypeptides represented by sequences ID no.14,16 and 18. Antibodies. Uses thereof.

3. Claims: 1c, 2c, 3c , 5c, 9c, 11C, 14c, 15c and (4, 6, 7, 8, 10, 12, 13, 16, 17, 18, 19, 20) partially

Mammalian iL-176. Polynucleotide represented by sequence ID no.27 and polypeptide represented by sequence ID no.28. Antibodies. Uses thereof.

4. Claims: 1d, 2d, 3d , 5d, 9d, 11D, 14d, 15d and (4, 6, 7, 8, 10, 12, 13, 16, 17, 18, 19, 20) partially

Mammalian iL-177. Polynucleotide represented by sequence ID no.29 and polypeptide represented by sequence ID no.30. Antibodies. Uses thereof.

INTERNATIONAL SEARCH REPORT

(Information on patent family members)

Int'l. Application No.

PCT/US 00/00006

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WO 9849310 A	05-11-1998	AU 7152798 A EP 0977861 A NO 995182 A	24-11-1998 09-02-2000 22-12-1999
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WO 9960127 A	25-11-1999	AU 3993799 A WO 9946281 A	06-12-1999 16-09-1999



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(21) International Application Number: PCT/US00/00006 (22) International Filing Date: 10 January 2000 (10.01.00) (30) Priority Data: 09/228,822 11 January 1999 (11.01.99) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Gal- loping Hill Road, Kenilworth, NJ 07033-0530 (US). (72) Inventors: GORMAN, Daniel, M.; 6371 Central Avenue, Newark, CA 94560 (US). BAZAN, J., Fernando; 775 Uni- versity Drive, Menlo Park, CA 94025 (US). KASTELEIN, Robert, A.; 463 Summit Drive, Redwood City, CA 94062 (US). (74) Agents: THAMPOE, Immac, J. et al.; Schering-Plough Cor- poration, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).			(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished</i> <i>upon receipt of that report.</i>
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EE	Estonia						

Description

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INTERLEUKIN-17 RELATED MAMMALIAN CYTOKINES. POLYNUCLEOTIDES ENCODING THEM. USES

FIELD OF THE INVENTION

The present invention relates to compositions related to proteins which function in controlling physiology, development, and differentiation of mammalian cells, e.g., cells of a mammalian immune system. In particular, it provides nucleic acids, proteins, antibodies, and mimetics which regulate cellular physiology, development, differentiation, or function of various cell types, including hematopoietic cells.

BACKGROUND OF THE INVENTION

The immune system of vertebrates consists of a number of organs and several different cell types. Two major cell types include the myeloid and lymphoid lineages. Among the lymphoid cell lineage are B cells, which were originally characterized as differentiating in fetal liver or adult bone marrow, and T cells, which were originally characterized as differentiating in the thymus. See, e.g., Paul (ed. 1998) Fundamental Immunology (4th ed.) Raven Press, New York.

In many aspects of the development of an immune response or cellular differentiation, soluble proteins known as cytokines play a critical role in regulating cellular interactions. These cytokines apparently mediate cellular activities in many ways. They have been shown, in many cases, to modulate proliferation, growth, and differentiation of hematopoietic stem cells into the vast number of progenitors composing the lineages responsible for an immune response.

However, the cellular molecules which are expressed by different developmental stages of cells in these maturation pathways are still incompletely identified. Moreover, the roles and mechanisms of action of signaling molecules which induce, sustain, or modulate the various physiological,

developmental, or proliferative states of these cells is poorly understood. Clearly, the immune system and its response to various stresses had relevance to medicine, e.g., infectious diseases, cancer related responses and treatment, allergic and transplantation rejection responses. See, e.g., Thorn, et al. Harrison's Principles of Internal Medicine McGraw/Hill, New York.

Medical science relies, in large degree, to appropriate recruitment or suppression of the immune system in effecting cures for insufficient or improper physiological responses to environmental factors. However, the lack of understanding of how the immune system is regulated or differentiates has blocked the ability to advantageously modulate the normal defensive mechanisms to biological challenges. Medical conditions characterized by abnormal or inappropriate regulation of the development or physiology of relevant cells thus remain unmanageable. The discovery and characterization of specific cytokines will contribute to the development of therapies for a broad range of degenerative or other conditions which affect the immune system, hematopoietic cells, as well as other cell types. The present invention provides solutions to some of these and many other problems.

SUMMARY OF THE INVENTION

The present invention is based, in part, upon the discovery of cDNA clones encoding various cytokine-like proteins which exhibit significant sequence similarity to the cytokine designated CTLA-8.

The invention embraces isolated genes encoding the proteins of the invention, variants of the encoded proteins, e.g., mutations (muteins) of the natural sequences, species and allelic variants, fusion proteins, chemical mimetics, antibodies, and other structural or functional analogs. Various uses of these different nucleic acid or protein compositions are also provided.

In certain nucleic acid embodiments, the invention provides an isolated or recombinant polynucleotide comprising sequence from: a) a mammalian IL-173, which: encodes at least 8 contiguous amino acids of SEQ ID NO: 6, 8, 10, or 12; encodes

5 at least two distinct segments of at least 5 contiguous amino
acids of SEQ ID NO: 6, 8, 10, or 12; or comprises one or more
segments at least 21 contiguous nucleotides of SEQ ID NO: 5, 7,
9, or 11; b) a mammalian IL-174, which: encodes at least 8
10 5 contiguous amino acids of SEQ ID NO: 14, 16, or 18; encodes at
least two distinct segments of at least 5 contiguous amino
acids of SEQ ID NO: 14, 16, or 18; or comprises one or more
segments at least 21 contiguous nucleotides of SEQ ID NO: 14,
15 16, or 18; c) a mammalian IL-176, which: encodes at least 8
10 contiguous amino acids of SEQ ID NO: 28; encodes at least two
distinct segments of at least 5 contiguous amino acids of SEQ
ID NO: 28; or comprises one or more segments at least 21
20 contiguous nucleotides of SEQ ID NO: 27; d) a mammalian IL-177,
which: encodes at least 8 contiguous amino acids of SEQ ID NO:
15 30; encodes at least two distinct segments of at least 5
contiguous amino acids of SEQ ID NO: 30; or comprises one or
more segments at least 21 contiguous nucleotides of SEQ ID NO:
25 29. Other embodiments include such a polynucleotide in an
expression vector, comprising sequence: a) (IL-173) which:
20 encodes at least 12 contiguous amino acids of SEQ ID NO: 6, 8,
10, or 12; encodes at least two distinct segments of at least 7
30 and 10 contiguous amino acids of SEQ ID NO: 6, 8, 10, or 12; or
comprises at least 27 contiguous nucleotides of SEQ ID NO: 5,
7, 9, 11; b) (IL-174) which: encodes at least 12 contiguous
25 amino acids of SEQ ID NO: 14, 16, or 18; encodes at least two
distinct segments of at least 7 and 10 contiguous amino acids
of SEQ ID NO: 14, 16, or 18; or comprises at least 27
contiguous nucleotides of SEQ ID NO: 13, 15, or 17; c) (IL-176)
40 which: encodes at least 12 contiguous amino acids of SEQ ID NO:
30 28; encodes at least two distinct segments of at least 7 and 10
contiguous amino acids of SEQ ID NO: 28; or comprises at least
27 contiguous nucleotides of SEQ ID NO: 27; or d) (IL-177)
45 which: encodes at least 12 contiguous amino acids of SEQ ID NO:
30 30; encodes at least two distinct segments of at least 7 and 10
contiguous amino acids of SEQ ID NO: 30; or comprises at least
27 contiguous nucleotides of SEQ ID NO: 29. Certain
embodiments will include those polynucleotides: a) (IL-173)
50 which: encode at least 16 contiguous amino acid residues of SEQ
ID NO: 6, 8, 10, or 12; encode at least two distinct segments

5 of at least 10 and 13 contiguous amino acid residues of SEQ ID
NO: 6, 8, 10, or 12; comprise at least 33 contiguous
nucleotides of SEQ ID NO: 5, 7, 9, or 11; or comprise the
entire mature coding portion of SEQ ID NO: 5, 7, 9, or 11; b)
10 5 (IL-174) which: encode at least 16 contiguous amino acid
residues of SEQ ID NO: 14, 16, or 18; encode at least two
distinct segments of at least 10 and 13 contiguous amino acid
residues of SEQ ID NO: 14, 16, or 18; comprise at least 33
15 contiguous nucleotides of SEQ ID NO: 13, 15, or 17; or comprise
10 the entire mature coding portion of SEQ ID NO: 13, 15, or 17;
c) (IL-176) which: encode at least 16 contiguous amino acids of
SEQ ID NO: 28; encode at least two distinct segments of at
20 least 10 and 14 contiguous amino acid residues of SEQ ID NO:
28; comprise at least 33 contiguous nucleotides of SEQ ID NO:
15 27; or comprise the entire mature coding portion of SEQ ID NO:
27; or d) (IL-177) which: encode at least 16 contiguous amino
acids of SEQ ID NO: 30; encode at least two distinct segments
25 of at least 10 and 14 contiguous amino acid residues of SEQ ID
NO: 30; comprise at least 33 contiguous nucleotides of SEQ ID
20 NO: 29; or comprise the entire mature coding portion of SEQ ID
NO: 29.

30 Various methods are provided, e.g., making: a) a
polypeptide comprising expressing the described expression
vector, thereby producing the polypeptide; b) a duplex nucleic
25 acid comprising contacting a described polynucleotide with a
35 complementary nucleic acid, thereby resulting in production of
the duplex nucleic acid; or c) a described polynucleotide
comprising amplifying using a PCR method.

40 Alternatively, the invention provides an isolated or
30 recombinant polynucleotide which hybridizes under stringent
wash conditions of at least 55° C and less than 400 mM salt to:
a) the described (IL-173) polynucleotide which consists of the
coding portion of SEQ ID NO: 5, 7, 9, or 11; b) the described
45 (IL-174) polynucleotide which consists of the coding portion of
5 (IL-174) polynucleotide which consists of the coding portion of
35 SEQ ID NO: 13, 15, or 17; the described (IL-176) polynucleotide
which consists of the coding portion of SEQ ID NO: 27; or d)
the described (IL-177) polynucleotide which consists of the
50 coding portion of SEQ ID NO: 29. Other embodiments include
such described polynucleotide: a) wherein the wash conditions

are at least 65° C and less than 300 mM salt; or b) which comprises at least 50 contiguous nucleotides of the coding portion of: SEQ ID NO: 5, 7, 9, or 11 (IL-173); SEQ ID NO: 13, 15, or 17 (IL-174); SEQ ID NO: 27 (IL-176); or SEQ ID NO: 29 (IL-177).

Certain kits are provided, e.g., comprising a described polynucleotide, and: a) instructions for the use of the polynucleotide for detection; b) instructions for the disposal of the polynucleotide or other reagents of the kit; or c) both a and b.

Various cells are provided also, e.g., a cell containing the described expression vector, wherein the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Polypeptide embodiments include, e.g., an isolated or recombinant antigenic polypeptide: a) (IL-173) comprising at least: i) one segment of 8 identical contiguous amino acids from SEQ ID NO: 6, 8, 10, or 12; or ii) two distinct segments of at least 5 contiguous amino acids from SEQ ID NO: 6, 8, 10, or 12; c) (IL-174) comprising at least: i) one segment of 8 identical contiguous amino acids from SEQ ID NO: 14, 16, or 18; or ii) two distinct segments of at least 5 contiguous amino acids from SEQ ID NO: 14, 16, or 18; c) (IL-176) comprising at least: i) one segment of 8 identical contiguous amino acids from SEQ ID NO: 28; or ii) two distinct segments of at least 5 contiguous amino acids from SEQ ID NO: 28; or d) (IL-177) comprising at least: i) one segment of 8 identical contiguous amino acids from SEQ ID NO: 30; or ii) two distinct segments of at least 5 contiguous amino acids from SEQ ID NO: 30.

Additional embodiments include such a described polypeptide, wherein: a) the segment of 8 identical contiguous amino acids is at least 14 contiguous amino acids; or b) one of the segments of at least 5 contiguous amino acids comprises at least 7 contiguous amino acids. Other embodiments include a described polypeptide, wherein: A) (IL-173) the polypeptide: a) comprises a mature sequence of SEQ ID NO: 6, 8, 10, or 12; b) binds with selectivity to a polyclonal antibody generated against an immunogen of a mature SEQ ID NO: 6, 8, 10, or 12; c)

comprises a plurality of distinct polypeptide segments of 10 contiguous amino acids of SEQ ID NO: 6, 8, 10, or 12; d) is a natural allelic variant of SEQ ID NO: 6, 8, 10, or 12; e) has a length at least 30 amino acids; or f) exhibits at least two non-overlapping epitopes which are selective for the mature SEQ ID NO: 6, 8, 10, or 12; B) (IL-174) the polypeptide: a) comprises mature SEQ ID NO: 14, 16, or 18; b) binds with selectivity to a polyclonal antibody generated against an immunogen of mature SEQ ID NO: 14, 16, or 18; c) comprises a plurality of distinct polypeptide segments of 10 contiguous amino acids of SEQ ID NO: 14, 16, or 18; d) has a length at least 30 amino acids; or e) exhibits at least two non-overlapping epitopes which are selective for mature SEQ ID NO: 14, 16, or 18; or D) (IL-176) the polypeptide: a) comprises SEQ ID NO: 28; b) binds with selectivity to a polyclonal antibody generated against an immunogen of SEQ ID NO: 28; c) comprises a plurality of distinct polypeptide segments of 10 contiguous amino acids of SEQ ID NO: 28; d) has a length at least 30 amino acids; or e) exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 28; or D) (IL-177) the polypeptide: a) comprises SEQ ID NO: 30; b) binds with selectivity to a polyclonal antibody generated against an immunogen of SEQ ID NO: 30; c) comprises a plurality of distinct polypeptide segments of 10 contiguous amino acids of SEQ ID NO: 30; d) has a length at least 30 amino acids; or e) exhibits at least two non-overlapping epitopes which are selective for primate protein of SEQ ID NO: 30. Various other embodiments include such a described polypeptide, which: a) is in a sterile composition; b) is not glycosylated; c) is denatured; d) is a synthetic polypeptide; e) is attached to a solid substrate; f) is a fusion protein with a detection or purification tag; g) is a 5-fold or less substitution from a natural sequence; or h) is a deletion or insertion variant from a natural sequence.

Methods of using described polypeptides are also provided, e.g.,: a) to label the polypeptide, comprising labeling the polypeptide with a radioactive label; b) to separate the polypeptide from another polypeptide in a mixture, comprising running the mixture on a chromatography matrix, thereby

5 separating the polypeptides; c) to identify a compound that
binds selectively to the polypeptide, comprising incubating the
compound with the polypeptide under appropriate conditions;
thereby causing the compound to bind to the polypeptide; or d)
10 5 to conjugate the polypeptide to a matrix, comprising
derivatizing the polypeptide with a reactive reagent, and
conjugating the polypeptide to the matrix.

15 Antibodies are also provided, including a binding compound
comprising an antigen binding portion from an antibody which
10 binds with selectivity to such a described polypeptide, wherein
the polypeptide: a) (IL-173) comprises the mature polypeptide
of SEQ ID NO: 6, 8, 10, or 12; b) (IL-174) comprises SEQ ID NO:
14, 16, or 18; c) (IL-176) comprises SEQ ID NO: 28; or d) (IL-
20 177) comprises SEQ ID NO: 30. Certain embodiments embrace such
15 a binding compound, wherein the antibody is a polyclonal
antibody which is raised against the polypeptide of: a) (IL-
173) SEQ ID NO: 6, 8, 10, or 12; b) (IL-174) SEQ ID NO: 14, 16,
25 or 18; c) (IL-176) SEQ ID NO: 28; or d) (IL-177) SEQ ID NO: 30.
Other embodiments include such a described binding compound,
20 wherein the: a) antibody: i) is immunoselected; ii) binds to a
denatured protein; or iii) exhibits a K_d to the polypeptide of
30 at least 30 mM; or b) the binding compound: i) is attached to a
solid substrate, including a bead or plastic membrane; ii) is
in a sterile composition; or iii) is detectably labeled,
25 including a radioactive or fluorescent label.

35 Methods are provided, e.g., producing an antigen:antibody
complex, comprising contacting a polypeptide comprising
sequence from SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 28, or 30
with a described binding compound under conditions which allow
40 30 the complex to form. Preferably, the binding compound is an
antibody, and the polypeptide is in a biological sample.

45 Kits are provided, e.g., comprising a described binding
compound and: a) a polypeptide of SEQ ID NO: 6, 8, 10, 12, 14,
16, 18, 28, or 30; b) instructions for the use of the binding
35 compound for detection; or c) instructions for the disposal of
the binding compound or other reagents of the kit.

50 And a method is provided of evaluating the selectivity of
binding of an antibody to a protein of SEQ ID NO: 6, 8, 10, 12,
14, 16, 18, 28, or 30, comprising contacting a described

antibody to the protein and to another cytokine; and comparing binding of the antibody to the protein and the cytokine.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

I. General

The present invention provides DNA sequence encoding various mammalian proteins which exhibit structural features characteristic of cytokines, particularly related to the cytokine designated CTLA-8 (also referred to as IL-17). Rat, mouse, human forms and a viral homolog of the CTLA-8 have been described and their sequences available from GenBank. See Rouvier, et al. (1993) J. Immunol. 150:5445-5456; Yao, et al. (1995) Immunity 3:811-821; Yao, et al. (1995) J. Immunol. 155:5483-5486; and Kennedy, et al. (1996) J. Interferon and Cytokine Res. 16:611-617. The CTLA-8 has activities implicated in arthritis, kidney graft rejection, tumorigenicity, virus-host interactions, and innate immunity; and appears to exhibit certain regulatory functions similar to IL-6. See PubMed (search for IL-17); Chabaud, et al. (1998) J. Immunol. 63:139-148; Amin, et al. (1998) Curr. Opin. Rheumatol. 10:263-268; Van Kooten, et al. (1998) J. Am. Soc. Nephrol. 9:1526-1534; Fossiez, et al. (1998) Int. Rev. Immunol. 16:541-551; Knappe, et al. (1998) J. Virol. 72:5797-5801; Seow (1998) Vet. Immunol. Immunopathol. 63:139-48; and Teunissen, et al. (1998) J. Invest. Dermatol. 111:645-649. A report on the signaling through the NF κ B transcription factor implicates a signal pathway which is used in innate immunity. Shalom-Barak, et al. (1998) J. Biol. Chem. 273:27467-27473.

The newly presented cDNA sequences exhibit various features which are characteristic of mRNAs encoding cytokines, growth factors, and oncogenes. Because the IL-17 is the first member of this newly recognized family of cytokines related to TGF- β , Applicants have designated the family IL-170, with the new members IL-172, IL-173, IL-174, IL-176, IL-177; and IL-171 and IL-175. The fold for this family is predicted to be that of the TGF- β family of cytokines. The TGF- β family of cytokines, and the IL-170 family share the common feature of a cystine knot motif, characterized by a particular spacing of

5 cysteine residues. See, e.g., Sun and Davies (1995) Ann. Rev. Biophys. Biomolec. Struct. 24:269-291; McDonald, et al. (1993) Cell 73:421-424; and Isaacs (1995) Curr. Op. Struct. Biol. 5:391-395. In particular, the structures suggest a number of
10 5 conserved cysteines, which correspond to, and are numbered, in human IL-172 (SEQ ID NO: 2), cysteines at 101, 103, 143, 156, and 158. The first cysteine corresponds to the position in Table 7 of human IL-172 (SEQ ID NO: 2) val19. The fourth
15 cysteine corresponds to that at mouse IL-172 (SEQ ID NO: 4) cys141; at human IL-173 (SEQ ID NO: 6) cys119; at mouse IL-174 (SEQ ID NO: 16) cys104; and at human IL-171 (SEQ ID NO: 21) cys50. The disulfide linkages should be cysteines 2 with 5;
20 and 3 with 6; and 1 with 4. Functional significance of the fold similarity suggests formation of dimers for the IL-170 family. As a consequence, IL-170 dimers would bring together
15 two cell surface receptors, through which signal transduction will occur.

25 These new proteins are designated CTLA-8 related, or generally IL-170, proteins. The natural proteins should be
20 capable of mediating various physiological responses which would lead to biological or physiological responses in target cells, e.g., those responses characteristic of cytokine
30 signaling. Initial studies had localized the message encoding this protein to various cell lines of hematopoietic cells. Genes encoding the original CTLA-8 (IL-17) antigen have been
35 mapped to mouse chromosome 1A and human chromosome 2q31. Murine CTLA-8 was originally cloned by Rouvier, et al. (1993) J. Immunol. 150:5445-5456. The human IL-173 has been mapped to chromosome 13q11. Similar sequences for proteins in other
40 30 mammalian species should also be available.

Purified CTLA-8, when cultured with synoviocytes, is able
45 to induce the secretion of IL-6 from these cells. This induction is reversed upon the addition of a neutralizing antibody raised against human CTLA-8. Endothelial, epithelial,
35 fibroblast and carcinoma cells also exhibit responses to treatment with CTLA-8. This data suggests that CTLA-8 may be implicated in inflammatory fibrosis, e.g., psoriasis,
50 sclerodermia, lung fibrosis, or cirrhosis. CTLA-8 may also cause proliferation of carcinomas or other cancer cells

inasmuch as IL-6 often acts as a growth factor for such cells. As such, the newly discovered other related family members are likely to have similar or related biological activities.

The descriptions below are directed, for exemplary purposes, to a murine or human IL-170 proteins, but are likewise applicable to related embodiments from other species.

II. Nucleic Acids

Tables 1-6 disclose the nucleotide and amino acid sequences of various new IL-170 family member sequences. The described nucleotide sequences and the related reagents are useful in constructing DNA clones useful for extending the clones in both directions for full length or flanking sequence determination, expressing IL-170 polypeptides, or, e.g., isolating a homologous gene from another natural source. Typically, the sequences will be useful in isolating other genes, e.g., allelic variants, from mouse, and similar procedures will be applied to isolate genes from other species, e.g., warm blooded animals, such as birds and mammals. Cross hybridization will allow isolation of genes from other species. A number of different approaches should be available to successfully isolate a suitable nucleic acid clone from other sources.

Table 1: Nucleotide sequence encoding a primate, e.g., human, IL-172 polypeptide and predicted amino acid sequence. Also can use complementary nucleic acid sequences for many purposes. Predicted signal cleavage site indicated, but may be a few residues on either side; putative glycosylation site at residues 55-57. SEQ ID NO: 1 and 2.

35	ATG GAC TGG CCT CAC AAC CTG CTG TTT CTT CTT ACC ATT TCC ATC TTC	48
	Met Asp Trp Pro His Asn Leu Leu Phe Leu Leu Thr Ile Ser Ile Phe	
	-20 -15 -10 -5	
40	CTG GGG CTG GGC CAG CCC AGG AGC CCC AAA AGC AAG AGG AAG GGG CAA	96
	Leu Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln	
	1 5 10	
45	GGG CGG CCT GGG CCC CTG GTC CCT GGC CCT CAC CAG GTG CCA CTG GAC	144
	Gly Arg Pro Gly Pro Leu Val Pro Gly Pro His Gln Val Pro Leu Asp	
	15 20 25	
45	CTG GTG TCA CGG ATG AAA CCG TAT GCC CGC ATG GAG GAG TAT GAG AGG	192
	Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg	
	30 35 40	

5	AAC ATC GAG GAG ATG GTG GCC CAG CTG AGG AAC AGC TCA GAG CTG GCC Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala 45 50 55 60	240
5	CAG AGA AAG TGT GAG GTC AAC TTG CAG CTG TGG ATG TCC AAC AAG AGG Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg 65 70 75	288
10	AGC CTG TCT CCC TGG GGC TAC AGC ATC AAC CAC GAC CCC AGC CGT ATC Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile 80 85 90	336
15	CCC GTG GAC CTG CCG GAG GCA CGG TGC CTG TGT CTG GGC TGT GTG AAC Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn 95 100 105	384
15	CCC TTC ACC ATG CAG GAG GAC CGC AGC ATG GTG AGC GTG CCG GTG TTC Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe 110 115 120	432
20	AGC CAG GTT CCT GTG CGC CGC CGC CTC TGC CCG CCA CCG CCC CGC ACA Ser Gln Val Pro Val Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr 125 130 135 140	480
20	GGG CCT TGC CGC CAG CGC GCA GTC ATG GAG ACC ATC GCT GTG GGC TGC Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys 145 150 155	528
25	ACC TGC ATC TTC TGA Thr Cys Ile Phe 160	543
30	MDWPHNLLFLLTISIFLGLG QPRSPKSKRKGGQGRPGPLVPGPHQVPLDLVSRMKPYARMEEYERN IEEMVAQLRNSSELAQRKCEVNLQWMSNKRSLSPWGYSHNDPSRIPIVDLPEARCLCLGCVPNFFT MQEDRSMVSVPVFSQVPVRRRLCPPPPRTGPCRQRAVMETIAVGCTCIF	
30	Particularly interesting segments include, e.g., those which begin or end with gln1; val19; pro20; pro22; lys34; pro35; leu78; ser79; glu98; ala99; phe110; thr111; cys143; or arg144.	
35	Nucleotide sequence encoding a rodent, e.g., mouse, IL-172 polypeptide and predicted amino acid sequence. Also can use complementary nucleic acid sequences for many purposes. Predicted signal cleavage site indicated, but may be a few residues on either side; putative glycosylation site at residues 53-55. SEQ ID NO: 3 and 4.	
40	ATG GAC TGG CCG CAC AGC CTG CTC TTC CTC CTG GCC ATC TCC ATC TTC Met Asp Trp Pro His Ser Leu Leu Phe Leu Leu Ala Ile Ser Ile Phe -22 -20 -15 -10	48
45	CTG GCG CCA AGC CAC CCC CGG AAC ACC AAA GGC AAA AGA AAA GGG CAA Leu Ala Pro Ser His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln -5 1 5 10	96
60	GGG AGG CCC AGT CCC TTG GCC CCT GGG CCT CAT CAG GTG CCG CTG GAC Gly Arg Pro Ser Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp 15 20 25	144
50	CTG GTG TCT CGA GTA AAG CCC TAC GCT CGA ATG GAA GAG TAT GAG CGG Leu Val Ser Arg Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg 30 35 40	192

5		AAC CTT GGG GAG ATG GTG GCC CAG CTG AGG AAC AGC TCC GAG CCA GCC	240
		Asn Leu Gly Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala	
	5	45 50 55	
		AAG AAG AAA TGT GAA GTC AAT CTA CAG CTG TGG TTG TCC AAC AAG AGG	288
		Lys Lys Lys Cys Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg	
		60 65 70	
10	10	AGC CTG TCC CCA TGG GGC TAC AGC ATC AAC CAC GAC CCC AGC CGC ATC	336
		Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile	
		75 80 85 90	
	15	CCT GCG GAC TTG CCC GAG GCG CGG TGC CTA TGT TTG GGT TGC GTG AAT	384
		Pro Ala Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn	
		95 100 105	
15	20	CCC TTC ACC ATG CAG GAG GAC CGT AGC ATG GTG AGC GTG CCA GTG TTC	432
		Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe	
		110 115 120	
		AGC CAG GTG CCG GTG CGC CGC CGC CTC TGT CCT CAA CCT CCT CGC CCT	480
		Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro	
		125 130 135	
20	25	GGG CCC TGC CGC CAG CGT GTC GTG ATG GAG ACC ATC GCT GTG GGT TGC	528
		Gly Pro Cys Arg Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys	
		140 145 150	
	30	ACC TGC ATC TTC TGA	543
		Thr Cys Ile Phe	
		155	
	35	MDWPHSLFLLAISIFLAPSHR RNTGKRRKGQGRPSPLAPGPHQVPLDLVSRVKPYARMEEYERN	
		LGEMVAQLRNSSEPAKKKCEVNLQLWLSNKRSLSPWGYSINHDPSRIPADLPEARCLCLGCVNPFT	
		MQEDRSMVSPVFSQVPVRRRLCPQPRPGPCRQVRVVMETIAVGCTCIF	
30		Particularly interesting segments include, e.g., those	
		which begin or end with arg1; ala17; pro18; pro20; his21;	
	40	lys32; pro33; leu76; ser77; glu96; ala97; phe108; thr109;	
		cys141; or arg142.	
	45	Table 2: Nucleotide sequence encoding a primate, e.g., human, IL-173	
35		polypeptide and predicted amino acid sequence. Also can use	
		complementary nucleic acid sequences for many purposes. SEQ ID NO: 5 and	
		6.	
	50	TGC GCG GAC CGG CCG GAG GAG CTA CTG GAG CAG CTG TAC GGG CGC CTG	48
		Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu	
		1 5 10 15	
40	55	GCG GCC GGC GTG CTC AGT GCC TTC CAC CAC ACG CTG CAG CTG GGG CCG	96
		Ala Ala Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro	
		20 25 30	
		CGT GAG CAG GCG CGC AAC GCG AGC TGC CCG GCA GGG GGC AGG CCC GCC	144
		Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala	
		35 40 45	
45	60	GAC CGC CGC TTC CGG ACG CCC ACC AAC CTG CGC AGC GTG TCG CCC TGG	192
		Asp Arg Arg Phe Arg Thr Pro Thr Asn Leu Arg Ser Val Ser Pro Trp	
		50 55 60	
	65	GCC TAC AGA ATC TCC TAC GAC CCG GCG AGG TAC CCC AGG TAC CTG CCT	240
		Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro	
		65 70 75 80	
50			
55			

5		GAA GCC TAC TGC CTG TGC CGG GGC TGC CTG ACC GGG CTG TTC GGC GAG	288
		Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu	
		85 90 95	
5		GAG GAC GTG CGC TTC CGC AGC GCC CCT GTC TAC ATG CCC ACC GTC GTC	336
		Glu Asp Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val	
		100 105 110	
10	10	CTG CGC CGC ACC CCC GCC TGC GCC GGC GGC CGT TCC GTC TAC ACC GAG	384
		Leu Arg Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu	
		115 120 125	
15	15	GCC TAC GTC ACC ATC CCC GTG GGC TGC ACC TGC GTC CCC GAG CCG GAG	432
		Ala Tyr Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu	
		130 135 140	
15		AAG GAC GCA GAC AGC ATC AAC T	454
		Lys Asp Ala Asp Ser Ile Asn	
20	20	145 150	
20	25	CADRPEELLEQLYGRLAAGVLSAFHHTLQLGPREQARNASCPAGGRPADDRFRFTPTNLRS	
		VSPWAYRISYDPARYPRYLPEAYCLCRGCLTGLFGEEDVRFERSAPVYMPTVVLRRTPACA	
		GGRSVYTEAYVTIPVGCTCVPEKADDSIN	
25		Supplementary nucleotide sequence encoding a primate, e.g.,	
		human, IL-173 polypeptide and predicted amino acid sequence.	
		Also can use complementary	
25	30	nucleic acid sequences for many purposes. SEQ ID NO: 7 and 8.	
25		gcccgggcag gtggcgacct cgctcagtcg gcttctcggt ccaagtcccc gggctctgg	58
		atg ctg gta gcc ggc ttc ctg ctg gcg ctg ccg ccg agc tgg gcc gcg	106
	35	Met Leu Val Ala Gly Phe Leu Leu Ala Leu Pro Pro Ser Trp Ala Ala	
		-15 -10 -5	
30		ggc gcc ccg agg gcg ggc agg cgc ccc gcg cgg ccg cgg ggc tgc gcg	154
	40	Gly Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala	
		-1 1 5 10 15	
		gac cgg ccg gag gag cta ctg gag cag ctg tac ggg cgc ctg gcg gcc	202
		Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala	
		20 25 30	
35	45	ggc gtg ctc agt gcc ttc cac cac acg ctg cag ctg ggg ccg cgt gag	250
		Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu	
		35 40 45	
	50	cag gcg cgc aac gcg agc tgc ccg gca ggg ggc agg ccc gcc gac cgc	298
		Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg	
		50 55 60	
40		cgc ttc ccg ccg ccc acc aac ctg cgc agc gtg tgc ccc tgg gcc tac	346
	55	Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr	
		65 70 75	
		aga atc tcc tac gac ccg gcg agg tac ccc agg tac ctg cct gaa gcc	394
	60	Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala	
		80 85 90 95	
45		tac tgc ctg tgc ccg ggc tgc ctg acc ggg ctg ttc ggc gag gag gac	442
		Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp	
		100 105 110	
	65	gtg cgc ttc cgc agc gcc cct gtc tac atg ccc acc gtc gtc ctg cgc	490
		Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg	
		115 120 125	
50			
55			

5 cgc acc ccc gcc tgc gcc ggc ggc cgt tcc gtc tac acc gag gcc tac 538
 Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
 130 135 140

5 gtc acc atc ccc gtg ggc tgc acc tgc gtc ccc gag ccg gag aag gac 586
 Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
 145 150 155

10 gca gac agc atc aac tcc agc atc gac aaa cag ggc gcc aag ctc ctg 634
 Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu
 160 165 170 175

15 ctg ggc ccc aac gac gcg ccc gct ggc ccc tgaggccggt cctgccccgg 684
 Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
 180 185

15 gaggtctccc cggccccgcat cccgaggcgc ccaagctgga gccgcctgga gggctcggtc 744

20 ggcgacctct gaagagagtg caccgagcaa accaagtgcc ggagcaccag cgccgccttt 804

20 ccatggagac tcgtaagcag cttcatctga cacgggcac cctggccttg ttttagctac 864

20 aagcaagcag cgtggctgga agctgatggg aaacgacccg gcacgggcat cctgtgtgag 924

25 gcccgcattg aggggttggg aaagtccacg gaggtccctt gaggagcctc tcagatcgcc 984

25 tgctgccccg gcagggcggt actcaccgct ggggtccttg caaagagata gggagcgata 1044

30 tgctttttta agcaatctaa aaataataat aagtatagcg actatatacc tactttttaa 1104

25 atcaactgtt ttgaatagag gcagagctat tttatattat caaatgagag ctactctgtt 1164

30 acatttctta acatataaac atcgtttttt acttctcttg gtagaatttt ttaaagcata 1224

35 attggaatcc ttggataaat tttgtagctg gtacactctg gcctgggtct ctgaattcag 1284

30 cctgtcaccg atggctgact gatgaaatgg acacgtctca tctgaccac tcttctctcc 1344

30 actgaaggtc ttcacgggccc tccaggcctc gtgccgaatt c 1385

40 MLVAGFLALPPSWAAGAPRAGRPPARPRGCADRPEELLEQLYGRLLAAGVLSAFHHTLQLGPREQARNA
 SCPAGGRPADRRFRPPTNLRVSFPAWRISYDPARYPRYLPEAYCLCRGCLTGLFGCEEDVRFRSAPVYM
 PTVVLRRTFACAGGRSVYTEAVTIFVGCTCVPEPEKADDSINSSIDKQAKLLLPNDAPAGP

35 45 Important predicted motifs include, e.g., CAMP PK at 50-53, 66-
 69, 72-75, and 113-116; Ca Phos at 82-84 and 166-168; myristoly
 sites at 57-61 and 164-166; phosphorylation sites at 50, 53,
 72, 75, 80, 82, 113, and 116.

50 Nucleotide sequence encoding a rodent, e.g., rat, IL-173
 40 polypeptide and predicted amino acid sequence. Also can use
 complementary nucleic acid sequences for many purposes. SEQ ID
 NO: 9 and 10.

55 TTT CCG AGA TAC CTG CCC GAA GCC TAC TGC CTG TGC CGA GGC TGT CTG 48
 Phe Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu
 1 5 10 15

45 60 ACC GGG CTC TAC GGT GAG GAG GAC TTC CGC TTT CGC AGC GCA CCC GTC 96
 Thr Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Ala Pro Val
 20 25 30

65 TTC TCT CCG GCG GTG GTG CTG CGG CGC ACG GCG GCC T 133
 Phe Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala
 35 40

50 FPRYLPEAYCLCRGCLTGLYGEEDFRFRSAPVFSAPVLRRTAA

5 Supplementary nucleotide sequence encoding a rodent, e.g., mouse, IL-173 polypeptide and predicted amino acid sequence. Also can use complementary nucleic acid sequences for many purposes. SEQ ID NO: 11 and 12.

5 atg ttg ggg aca ctg gtc tgg atg ctc ctc gtc ggc ttc ctg ctg gca 48
Met Leu Gly Thr Leu Val Trp Met Leu Leu Val Gly Phe Leu Leu Ala
-20 -15 -10

10 ctg gcg ccg ggc cgc gcg gcg ggc gcg ctg agg acc ggg agg cgc ccg 96
Leu Ala Pro Gly Arg Ala Ala Gly Ala Leu Arg Thr Gly Arg Arg Pro
-5 -1 1 5

15 gcg cgg ccg cgg gac tgc gcg gac ccg cca gag gag ctc ctg gag cag 144
Ala Arg Pro Arg Asp Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln
10 15 20

20 ctg tac ggg cgg ctg gcg gcc ggc gtg ctc agc gcc ttc cac cac acg 192
Leu Tyr Gly Arg Leu Ala Ala Gly Val Leu Ser Ala Phe His His Thr
25 30 35 40

25 ctg cag ctc ggg ccg cgc gag cag gcg cgc aat gcc agc tgc ccg gcc 240
Leu Gln Leu Gly Pro Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala
45 50 55

30 ggg ggc agg gcc gcc gac cgc cgc ttc ccg cca ccc acc aac ctg cgc 288
Gly Gly Arg Ala Ala Asp Arg Arg Phe Arg Pro Pro Thr Asn Leu Arg
60 65 70

35 agc gtg tgc ccc tgg gcg tac agg att tcc tac gac cct gct cgc ttt 336
Ser Val Ser Pro Trp Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Phe
75 80 85

40 ccg agg tac ctg ccc gaa gcc tac tgc ctg tgc cga gcc tgc ctg acc 384
Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr
90 95 100

45 ggg ctc tac ggg gag gag gac ttc cgc ttt cgc agc aca ccc gtc ttc 432
Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Thr Pro Val Phe
105 110 115 120

50 tct cca gcc gtg gtg ctg cgg cgc aca gcg gcc tgc gcg ggc gcc cgc 480
Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala Cys Ala Gly Gly Arg
125 130 135

55 tct gtg tac gcc gaa cac tac atc acc atc ccg gtg gcc tgc acc tgc 528
Ser Val Tyr Ala Glu His Tyr Ile Thr Ile Pro Val Gly Cys Thr Cys
140 145 150

60 gtg ccc gag ccg gac aag tcc gcg gac agt gcg aac tcc agc atg gac 576
Val Pro Glu Pro Asp Lys Ser Ala Asp Ser Ala Asn Ser Ser Met Asp
155 160 165

65 aag ctg ctg ctg ggg ccc gcc gac agg cct gcg ggg cgc tgatgccggg 625
Lys Leu Leu Leu Gly Pro Ala Asp Arg Pro Ala Gly Arg
170 175 180

70 gactgcccgc catggcccag ctctctgcat gcatcaggtc ccctggccct gacaaaaccc 685
accccatgat ccctggccgc tgccctaattt ttccaaaagg acagctacat aagcttttaa 745
tataatttttc aaagtagaca ctacatatct acaactattt tgaatagtgg cagaaactat 805
tttcatatta gtaatttaga gcaagcatgt tgttttttaa ctctcttgat atacaagcac 865
atcacacaca tcccgttttc ctctagtagg attcttgagt gcataattgt agtgcctcaga 925
tgaacttccct tctgctgcac tgtgccctgt ccctgagctc ctctctgtggc ccaagcttac 985
taagggtgata atgagtgtc cggtatctggg cacctaaggt ctccagggtcc ctggagaggg 1045

5 agggatgtgg gggggctagg aaccaagcgc ccccttggtc tttagcttat ggatggtcctt 1105
aactttataa agattaaagt ttttggtgtt attctttc 1143

5

MLGTLVWMLLVGFLALAPGRAAGALRTGRRPARPRDCADRPEELLEQLYGRILAAGVLSAFHHTLQLGPRE
QARNASCPAGGRAADRRFRPPTNLRVSVPWAYRISYDPAFPRLPEAYCLCRGCLTGLYGEEDFRFRSTP
VFSPAUVLRRTAACAGGRSVYAEHYITIPVGCTCVPEPKSADSANSMDKLLLGPAADRPAGR.

10

10 Important predicted motifs include, e.g., cAMP PK sites at 50-53,
66-69, 72-75, and 113-116; Ca phosphorylation sites at 82-84, 159-
161, and 166-168; myristoly sites at 57-61 and 101-105; N-glycosyl
sites at 51-53 and 164-166; phosphorylation sites at 50, 53, 72, 75,
80, 82, 113, and 116; and PKC phosphorylation sites at 4-6

15

15

Table 3: Nucleotide sequence encoding a primate, e.g., human, IL-174
polypeptide and predicted amino acid sequence. Also can use complementary
nucleic acid sequences for many purposes. SEQ ID NO: 13 and 14.

20

tgagtgtgca gtgccagc atg tac cag gtg gtt gca ttc ttg gca atg gtc 51
Met Tyr Gln Val Val Ala Phe Leu Ala Met Val
-15 -10

20

25 atg gga acc cac acc tac agc cac tgg ccc agc tgc tgc ccc agc aaa 99
Met Gly Thr His Thr Tyr Ser His Trp Pro Ser Cys Cys Pro Ser Lys
-5 -1 1 5 10

25

30 ggg cag gac acc tct gag gag ctg ctg agg tgg agc act gtg cct gtg 147
Gly Gln Asp Thr Ser Glu Glu Leu Leu Arg Trp Ser Thr Val Pro Val
15 20 25

cct ccc cta gag cct gct agg ccc aac cgc cac cca gag tcc tgt agg 195
Pro Pro Leu Glu Pro Ala Arg Pro Asn Arg His Pro Glu Ser Cys Arg
30 35 40

30

gcc agt gaa gat gga ccc ctc aac agc agg gcc atc tcc ccc tgg aga 243
Ala Ser Glu Asp Gly Pro Leu Asn Ser Arg Ala Ile Ser Pro Trp Arg
45 50 55

40 tat gag ttg gac aga gac ttg aac cgg ctc ccc cag gac ctg tac cac 291
Tyr Glu Leu Asp Arg Arg Leu Asn Arg Leu Pro Gln Asp Leu Tyr His
60 65 70 75

35

45 gcc cgt tgc ctg tgc cgc cac tgc gtc agc cta cag aca ggc tcc cac 339
Ala Arg Cys Leu Cys Pro His Cys Val Ser Leu Gln Thr Gly Ser His
80 85 90

50 atg gac ccc cgg ggc aac tcg gag ctg ctc tac cac aac cag act gtc 387
Met Asp Pro Arg Gly Asn Ser Glu Leu Leu Tyr His Asn Gln Thr Val
95 100 105

40

55 ttc tac cgg cgg cca tgc cat ggc gag aag ggc acc cac aag ggc tac 435
Phe Tyr Arg Arg Pro Cys His Gly Glu Lys Gly Thr His Lys Gly Tyr
110 115 120

tgc ctg gag cgc agg ctg tac cgt gtt tcc tta gct tgt gtg tgt gtg 483
Cys Leu Glu Arg Arg Leu Tyr Arg Val Ser Leu Ala Cys Val Cys Val
125 130 135

45

60

cgg ccc cgt gtg atg ggc tag 504
Arg Pro Arg Val Met Gly
140 145

65

MYQVVAFLAMVMGTHYSHWPSCCPSKGQDTSEELLRWSTVPVPPLEPARPNRHPESCRAEDGPL
NSRAISPWRYELDRDLNRLPDLYHARCLCPHCVSLQTGSHMDPRGNSELLYHNQTVFYRRPCHGE
KGTHKGYCLERRLYRVSLACVCVRPRVMG

50

55

5 Important predicted motifs include, e.g., cAMP PK sites at 21-24, 53-56, and 95-98; Ca phosphorylation sites at 15-17, 16-18, and 45-47; myristoyl sites at 12-16, 115-119, and 118-122; N-glycosyl site at 104-107; phosphorylation sites at 21, 23, 43, 53, 56, 95, 98, and 131; PKC phosphorylation sites at 41-43 and 119-121; and tyrosine kinase site at 95-102.

10 Nucleotide sequence encoding a rodent, e.g., mouse, IL-174 polypeptide and predicted amino acid sequence. Also can use complementary nucleic acid sequences for many purposes. SEQ ID NO: 15 and 16.

15

15 CGG CAC AGG CGG CAC AAA GCC CGG AGA GTG GCT GAA GTG GAG CTC TGC 48
Arg His Arg Arg His Lys Ala Arg Arg Val Ala Glu Val Glu Leu Cys
1 5 10 15

20 ATC TGT ATC CCC CCC AGA GCC TCT GAG CCA CAC CCA CCA CGC AGA ATC 96
Ile Cys Ile Pro Pro Arg Ala Ser Glu Pro His Pro Pro Arg Arg Ile
20 25 30

20 CTG CAG GGC CAG CAA GGA TGG CCT CTC AAC AGC AGG GCC ATC TCT CCT 144
Leu Gln Gly Gln Gln Gly Trp Pro Leu Asn Ser Arg Ala Ile Ser Pro
35 40 45

25 TGG AGC TAT GAG TTG GAC AGG GAC TTG AAT CGG GTC CCC CAG GAC TGG 192
Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp Trp
50 55 60

25 TAC CAC GCT CGA TGC CTG TGC CCA CAC TGC GTC ACG CTA CAG ACA GGC 240
Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Thr Leu Gln Thr Gly
65 70 75 80

30 TCC CAC ATG GAC CCG CTG GGC AAC TCC GTC CCA CTT TAC CAC AAC CAG 288
Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn Gln
85 90 95

30 ACG GTC TTC TAC CGG CGG CCA TGC ATG GCG AGG AAG GTA CCC ATC GCC 336
Thr Val Phe Tyr Arg Arg Pro Cys Met Ala Arg Lys Val Pro Ile Ala
100 105 110

35 GCT ACT GCT TGG AGC GCA GGT CTA CCG AGT CTC CTT GGC TTG TGT GTG 384
Ala Thr Ala Trp Ser Ala Gly Leu Pro Ser Leu Leu Gly Leu Cys Val
115 120 125

45 TGT GCG GCC CCG GGT CAT GGC TTA GTC ATG CTC ACC ATC TGC CTG AGG 432
Cys Ala Ala Pro Gly His Gly Leu Val Met Leu Thr Ile Cys Leu Arg
130 135 140

40 TGAATGCCGG GTGGGAGAGA GGGCCAGGTG TACATCACCT GCCAATGCCGG GCCGGGTTCA 492

AGCCTGCAAA GCCTACCTGA AGCAGCAGGT CCCGGGACAG GATGGAGACT TGGGGAGAAA 552

55 TCTGACTTTT GCACTTTTGT GAGCATTTTG GGAAGAGCAG GTTCGCTTGT GCTGTAGAGA 612

TGCTGTTG 620

45 RRRRHKARRVAEVELCICIPPRASEPHPPRRILQGQGGWFLNSRAISFWSYELDRDLNRVPQDWYHARC

60 LCPHCVTLTGTGSHMDPLGNSVPLYHNQTVFYRRPCMARKVFIAATAWSAGLPSLLGLCVCAAPGHGLVM
LTICLR

5 Supplementary nucleotide sequence encoding a rodent, e.g.,
mouse, IL-174 polypeptide and predicted amino acid sequence.
Also can use complementary nucleic acid sequences for many
purposes. SEQ ID NO: 17 and 18.

5
atg tac cag gct gtt gca ttc ttg gca atg atc gtg gga acc cac acc 48
Met Tyr Gln Ala Val Ala Phe Leu Ala Met Ile Val Gly Thr His Thr
-15 -10 -5 -1

10
gtc agc ttg cgg atc cag gag ggc tgc agt cac ttg ccc agc tgc tgc 96
Val Ser Leu Arg Ile Gln Glu Gly Cys Ser His Leu Pro Ser Cys Cys
1 5 10 15

15
ccc agc aaa gag caa gaa ccc ccg gag gag tgg ctg aag tgg agc tct 144
Pro Ser Lys Glu Gln Glu Pro Pro Glu Glu Trp Leu Lys Trp Ser Ser
20 25 30

20
gca tct gtg tcc ccc cca gag cct ctg agc cac acc cac cac gca gaa 192
Ala Ser Val Ser Pro Pro Glu Pro Leu Ser His Thr His His Ala Glu
35 40 45

25
tcc tgc agg gcc agc aag gat ggc ccc ctc aac agc agg gcc atc tct 240
Ser Cys Arg Ala Ser Lys Asp Gly Pro Leu Asn Ser Arg Ala Ile Ser
50 55 60

30
cct tgg agc tat gag ttg gac agg gac ttg aat cgg gtc ccc cag gac 288
Pro Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp
65 70 75 80

35
ctg tac cac gct cga tgc ctg tgc cca cac tgc gtc agc cta cag aca 336
Leu Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Ser Leu Gln Thr
85 90 95

40
ggc tcc cac atg gac ccg ctg ggc aac tcc gtc cca ctt tac cac aac 384
Gly Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn
100 105 110

45
cag acg gtc ttc tac cgg cgg cca tgc cat ggt gag gaa ggt acc cat 432
Gln Thr Val Phe Tyr Arg Arg Pro Cys His Gly Glu Glu Gly Thr His
115 120 125

50
cgc cgc tac tgc ttg gag cgc agg ctc tac cga gtc tcc ttg gct tgt 480
Arg Arg Tyr Cys Leu Glu Arg Arg Leu Tyr Arg Val Ser Leu Ala Cys
130 135 140

55
gtg tgt gtg cgg ccc cgg gtc atg gct tagtcatgct caccacctgc 527
Val Cys Val Arg Pro Arg Val Met Ala
145 150

60
ctgaggctga tgcccgggttg ggagagaggg ccagggtgtac aatcaccttg ccaatgcggg 587
ccgggttcaa gccctccaaa gccctacctg aagcagcagg ctcccgggac aagatggagg 647
acttggggag aaactctgac ttttgcactt tttggaagca cttttgggaa ggagcagggtt 707
ccgcttgtgc tgctagagga tgctgttgtg gcatttctac tcaggaacgg actccaaagg 767
cctgctgacc ctggaagcca tactcctggc tcctttcccc tgaatcccc aactcctggc 827
acaggcactt tctccacctc tcccccttg ccttttgttg tgtttgttg tgcattgcaa 887
ctctgcgtgc agccagggtt aattgccttg aaggatgggt ctgaggtgaa agctgttatc 947
gaaagtgaag agatttatcc aaataaacat ctgtgttt 985

65
MYQAVAFAMIVGTHTVSLRIQEGCSHLPSCCPSKEPPEEWLKWSSASVSPPEPLSHTHAESCRAS
KDGPLNSRAISFWSYELDRDLNRVPQDLYHARCLCPHCVSLQTGSHMDPLGNSVPLYHNQTVFYRRPCH
GEEGTHRRYCLERRLYRVSLACVCVRPRVMA

5 Important predicted motifs include, e.g., cAMP PK sites at 29-32 and 61-64; Ca phosphorylation sites at 18-20, 53-55, and 67-69; myristoyl site at 123-127; N-glycosylation site at 112-114; and phosphorylation sites at 29, 31, 51, 53, 61, 64, 139, and 141; and PKC phosphorylation sites at 2-4, 49-51, and 127-129.

10 Table 4: Nucleotide sequence encoding a primate, e.g., human, IL-171 under IUPAC code. Also can use complementary nucleic acid sequences for many purposes. SEQ ID NO: 19:

15	15	GACACGGATG AGGACCGCTA TCCACAGAAG CTGGCCTTCG CCGAGTGCCT GTGCAGAGGC	60
		TGTATCGATG CACGGACGGG CCGCGAGACA GCTGCGCTCA ACTCCGTGCG GCTGCTCCAG	120
		AGCCTGCTGG TGCTGCGCCG CCGGCCCTGC TCCCGCGACG GCTCGGGGCT CCCCACACCT	180
		GGGGCCTTTG CCTTCCACAC CGAGTTCATC CACGTCCCCG TCGGCTGCAC CTGCGTGCTG	240
20	20	CCCCGTTCAA GTGTGACCGC CAAGGCCGTG GGGCCCTTAG NTGACACCGT GTGCTCCCCA	300
		GAGGGACCCC TATTATGGG AATTATGGTA TTATATGCTT CCCACATACT TGGGGCTGGC	360
	25	ATCCCGNGCT GAGACAGCCC CCTGTTCTAT TCAGCTATAT GGGGAGAAGA GTAGACTTTC	420
		AGCTAAGTGA AAAGTGNAAC GTGCTGACTG TCTGCTGTCG TNCTACTNAT GCTAGCCCGA	480
25	30	GTGTTCACTC TGAGCCTGTT AAATATAGGC GGTATGTAC C	521

SEQ ID NO: 20 and 21 are PATENTIN translatable cDNA and polypeptide sequences:

30	35	GAC ACG GAT GAG GAC CGC TAT CCA CAG AAG CTG GCC TTC GCC GAG TGC	48
		Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu Cys	
		1 5 10 15	
	40	CTG TGC AGA GGC TGT ATC GAT GCA CGG ACG GGC CGC GAG ACA GCT GCG	96
		Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala	
		20 25 30	
35	45	CTC AAC TCC GTG CGG CTG CTC CAG AGC CTG CTG GTG CTG CGC CGC CGG	144
		Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg	
		35 40 45	
	50	CCC TGC TCC CGC GAC GGC TCG GGG CTC CCC ACA CCT GGG GCC TTT GCC	192
		Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala	
		50 55 60	
40		TTC CAC ACC GAG TTC ATC CAC GTC CCC GTC GGC TGC ACC TGC GTG CTG	240
		Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu	
		65 70 75 80	
	55	CCC CGT TCA AGT GTG ACC GCC AAG GCC GTG GGG CCC TTA GAT GAC ACC	288
		Pro Arg Ser Ser Val Thr Ala Lys Ala Val Gly Pro Leu Xaa Asp Thr	
		85 90 95	
45	60	GTG TGC TCC CCA GAG GGA CCC CTA TTT ATG GGA ATT ATG GTA TTA TAT	336
		Val Cys Ser Pro Glu Gly Pro Leu Phe Met Gly Ile Met Val Leu Tyr	
		100 105 110	
	65	GCT TCC CAC ATA CTT GGG GCT GGC ATC CCG nGC TGAGACAGCC CCCTGTTCTA	389
		Ala Ser His Ile Leu Gly Ala Gly Ile Pro Xaa	
50		115 120	
		TTCAGCTATA TGGGGAGAAG AGTAGACTTT CAGCTAAGTG AAAAGTGCAA CGTGCTGACT	449

5 GTCTGCTGTC GTCCTACTCA TGCTAGCCCG AGTGTTCCT CTGAGCCTGT TAAATATAGG 509
 CCGTTATGTA CC 521

5 DTDEDYPOKLAFAECLCRGCIDARTGRETAALNSVRLQLSLLVLRRLRRRPCSRDGSGLPTPGAFHFTEFI
 HVPVGCTCVLPSSVTAKAVGPLXDTVCSPGGLFMGINVLYASHILGAGIPX

10 Supplementary nucleotide sequence encoding a primate, e.g., human,
 IL-171. Also can use complementary nucleic acid sequences for many
 purposes. SEQ ID NO: 22 and 23:

10 gtgtggcctc aggtataaga gcggctgctg ccagggtgcat gcccagggtgc acctgtggga 60
 15 ttgccgccag gtgtgcaggc cgctccaagc ccagcctgcc ccgctgccgc cacc atg 117
 Met

20 acg ctc ctc ccc ggc ctc ctg ttt ctg acc tgg ctg cac aca tgc ctg 165
 Thr Leu Leu Pro Gly Leu Leu Phe Leu Thr Trp Leu His Thr Cys Leu
 -15 -10 -5 -1

20 gcc cac cat gac ccc tcc ctc agg ggg cac ccc cac agt cac ggt acc 213
 25 Ala His His Asp Pro Ser Leu Arg Gly His Pro His Ser His Gly Thr
 1 5 10 15

cca cac tgc tac tcg gct gag gaa ctg ccc ctc ggc cag gcc ccc cca 261
 Pro His Cys Tyr Ser Ala Glu Glu Leu Pro Leu Gly Gln Ala Pro Pro
 20 25 30

25 cac ctg ctg gct cga ggt gcc aag tgg ggg cag gct ttg cct gta gcc 309
 His Leu Leu Ala Arg Gly Ala Lys Trp Gly Gln Ala Leu Pro Val Ala
 35 40 45

35 ctg gtg tcc agc ctg gag gca gca agc cac agg ggg agg cac gag agg 357
 Leu Val Ser Ser Leu Glu Ala Ala Ser His Arg Gly Arg His Glu Arg
 50 55 60

30 ccc tca gct acg acc cag tgc ccg gtg ctg cgg ccg gag gag gtg ttg 405
 40 Pro Ser Ala Thr Thr Gln Cys Pro Val Leu Arg Pro Glu Glu Val Leu
 65 70 75 80

gag gca gac acc cac cag cgc tcc atc tca ccc tgg aga tac cgt gtg 453
 45 Glu Ala Asp Thr His Gln Arg Ser Ile Ser Pro Trp Arg Tyr Arg Val
 85 90 95

35 gac acg gat gag gac cgc tat cca cag aag ctg gcc ttc gcc gag tgc 501
 50 Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu Cys
 100 105 110

ctg tgc aga ggc tgt atc gat gca cgg acg ggc cgc gag aca gct gcg 549
 40 Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala
 115 120 125

55 ctc aac tcc gtg cgg ctg ctc cag agc ctg ctg gtg ctg cgc cgc cgg 597
 Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg
 130 135 140

45 ccc tgc tcc cgc gac ggc tcg ggg ctc ccc aca cct ggg gcc ttt gcc 645
 60 Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala
 145 150 155 160

ttc cac acc gag ttc atc cac gtc ccc gtc ggc tgc acc tgc gtg ctg 693
 65 Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu
 165 170 175

ccc cgt tca gtg tgaccgccga ggccgtgggg cccttagact ggacacgtgt 745
 50 Pro Arg Ser Val
 180

70

5	gtccccaga gggcaccccc tatttatgtg tatttattgg tatttatatg cctcccccaa 805	
	cactaccctt ggggtctggg cattccccgt gtctggagga cageccccca ctgttctcct 865	
5	catctccagc ctcagtagtt gggggtagaa ggagctcagc acctcttcca gcccttaaag 925	
	ctgcagaaaa ggtgtcacac ggctgcctgt acctgggtc cctgtcctgc tcccggttc 985	
10	ccttacccta tcaactggcct caggccccg caggctgcct cttcccaacc tccttggag 1045	
10	taccctgtt tcttaacaa ttatttaagt gtacgtgtat tattaactg atgaacacat 1105	
	cc 1107	
15	MTLLPGLLFLTLHTCLAHHDPSLRGHPHSHGTPhcysAEELPLGQAPPHLLARGAKWGQALFVALVSS	
	LEAASHRGRHERPSATTQCPVLRPEEVLEADTHQRSISPWRYRVDDEDYRQKLAFACLRCGICIDAR	
	TGRETAALNSVRLQLSLVLRPPSRDGSGLPTPGAFHFTEFIHVPVGCTCVLPRSV	
20	Table 5: Nucleotide sequence encoding a primate, e.g., human, IL-175	
20	sequence under IUPAC code. Also can use complementary nucleic acid	
	sequences for many purposes. SEQ ID NO: 24:	
25	GAGAAAGAGC TTCCTGCACA AAGTAAGCCA CCAGCGCAAC ATGACAGTGA AGACCCTGCA 60	
	TGGCCCAGCC ATGGTCAAGT ACTTGCTGCT GTCGATATTG GGGCTTGCCT TTCTGAGTGA 120	
30	GGCGGCAGCT CGGAAAATCC CCAAAGTAGG ACATACTTTT TTCCAAAAGC CTGAGAGTTG 180	
25	CCCGCCTGTG CCAGGAGSTA GTATGAAGCT TGACATGGC ATCATCAATG AAAACCAGCG 240	
	CGTTTCCATG TCACGTAACA TCGAGAGCCG CTCCACCTCC CCCTGGAATT AACTGTGCAC 300	
35	TTGGGACCCC AACCGGTACC CCTCGAAGTT GTACAGGCC AAGTGTAGGA ACTTGGGCTG 360	
30	TATCAATGCT CAAGGAAAGG AAGACATCTN CATGAATTCC GTC 403	
40	SEQ ID NO: 25 and 26 are PATENTIN translatable cDNA and polypeptide	
	sequences. Predicted signal cleavage site indicated, but may be a	
	few residues on either side; putative glycosylation site at residues	
	53-55:	
35	45 GAGAAAGAGC TTCCTGCACA AAGTAAGCCA CCAGCGCAAC ATGACAGTGA AGACCCTGCA 60	
	TGCCCCAGCC ATG GTC AAG TAC TTG CTG CTG TCG ATA TTG GGG CTT GCC 109	
	Met Val Lys Tyr Leu Leu Leu Ser Ile Leu Gly Leu Ala	
	-20 -15 -10	
50	TTT CTG AGT GAG GCG GCA GCT CGG AAA ATC CCC AAA GTA GGA CAT ACT 157	
40	Phe Leu Ser Glu Ala Ala Ala Arg Lys Ile Pro Lys Val Gly His Thr	
	-5 1 5	
55	TTT TTC CAA AAG CCT GAG AGT TGC CCG CCT GTG CCA GGA GGT AGT ATG 205	
	Phe Phe Gln Lys Pro Glu Ser Cys Pro Pro Val Pro Gly Gly Ser Met	
	10 15 20 25	
45	AAG CTT GAC ATT GGC ATC ATC AAT GAA AAC CAG CGC GTT TCC ATG TCA 253	
60	Lys Leu Asp Ile Gly Ile Ile Asn Glu Asn Gln Arg Val Ser Met Ser	
	30 35 40	
65	CGT AAC ATC GAG AGC CGC TCC ACC TCC CCC TGG AAT TAC ACT GTC ACT 301	
	Arg Asn Ile Glu Ser Arg Ser Thr Ser Pro Trp Asn Tyr Thr Val Thr	
	45 50 55	
50	TGG GAC CCC AAC CGG TAC CCC TCG AAG TTG TAC AGG CCC AAG TGT AGG 349	
	Trp Asp Pro Asn Arg Tyr Pro Ser Lys Leu Tyr Arg Pro Lys Cys Arg	
	60 65 70	
55		

5 AAC TTG GGC TGT ATC AAT GCT CAA GGA AAG GAA GAC ATC TCC ATG AAT 397
 Asn Leu Gly Cys Ile Asn Ala Gln Gly Lys Glu Asp Ile Ser Met Asn
 75 80 85

5 TCC GTC 403
 Ser Val
 90

10 MVKYLLLSILGLAFLSEAAARKIPKVGHTFFQKPESCPFPVGGSMKLDIGIINENQVRMSRNIESRST
 SPWNYTWTWDPNRYPSKLYRPKCRNLGCINAQKEDIXMNSV

15 Particularly interesting segments include, e.g., those
 which begin or end with arg1; cys17; pro18, pro19; val20;
 thr49; ser50; arg69; pro70; and the end of the sequence
 available.

20 Table 6: Nucleotide sequence encoding a primate, e.g., human,
 IL-176. Also can use complementary nucleic acid sequences for
 many purposes. SEQ ID NO: 27 and 28:

20 tc gtg ccg tat ctt ttt aaa aaa att att ctt cac ttt ttt gcc tcc 47
 Val Pro Tyr Leu Phe Lys Lys Ile Ile Leu His Phe Phe Ala Ser
 1 5 10 15

25 tat tac ttg tta ggg aga ccc aat ggt agt ttt att cct tgg gga tac 95
 Tyr Tyr Leu Leu Gly Arg Pro Asn Gly Ser Phe Ile Pro Trp Gly Tyr
 20 25 30

25 ata gta aat act tca tta aag tcg agt aca gaa ttt gat gaa aag tgt 143
 Ile Val Asn Thr Ser Leu Lys Ser Ser Thr Glu Phe Asp Glu Lys Cys
 35 40 45

30 gga tgt gtg gga tgt act gcc gcc ttc aga agt cca cac act gcc tgg 191
 Gly Cys Val Gly Cys Thr Ala Ala Phe Arg Ser Pro His Thr Ala Trp
 50 55 60

35 agg gag aga act gct gtt tat tca ctg att aag cat ttg ctg tgt acc 239
 Arg Glu Arg Thr Ala Val Tyr Ser Leu Ile Lys His Leu Leu Cys Thr
 65 70 75

40 aac tac ttt tca tgt ctt atc tta att ctc ata aca gtc att 281
 Asn Tyr Phe Ser Cys Leu Ile Leu Ile Leu Thr Val Ile
 80 85 90

45 tgatatattta aaaaacccca gaaatctgag aaagagataa agtggtttgc tcaaggttat 341
 agaacagact accatgtgtt gtatttcaga ttttaattca tgtttctctg attttaagtt 401

50 ttgttcgctt gccagggtac cccacaaaaa tgccaggcag ggcattttca tgatgcactt 461
 gagatacctg aaatgacagg gtagcatcac acctgagagg ggtaaaggat gggaacctac 521

55 cttccatggc cgctgcttgg cagtctcttg ctgcatgcta gcagagccac tgtatatgtg 581
 ccgaggctct gagaattaac tgcttaaga actgccttct ggagggagaa gagcacaaga 641

45 tcacaattaa ccatatacac atcttactgt gcgaggtcat tgagcaatac aggagggatt 701

60 ttatacattt tagcaactat cttcaaaacc tgagctatag ttgtattctg ccccttctct 761
 ctgggcaaaa gtgtaaaagt ttg 784

65 VPYLFKKIILHFFASYILLGRPNFSFIPWGYIVNTSLKSSTEFDEKCGCVGCTAAAFSPHTAWRER
 TAVYSLIKHLCTNYPSCILILITVI

5 Nucleotide sequence encoding a primate, e.g., human, IL-177.
Also can use complementary nucleic acid sequences for many
purposes. SEQ ID NO: 29 and 30:

```

5   gtg act gta ttg tgg gga cag gaa gca caa att ccc atg tgg atc act   48
    Val Thr Val Leu Trp Gly Gln Glu Ala Gln Ile Pro Met Trp Ile Thr
    1       5       10      15
10  agg aga gat aat aag tgg ggt cat ttc acc cct tgg tcc cct gct tcc   96
    Arg Arg Asp Asn Lys Trp Gly His Phe Thr Pro Trp Ser Pro Ala Ser
    20      25      30
15  aga ccc aaa gag gcc tac atg gca ttg tgc ttc ctt ctt agt tgt agg   144
    Arg Pro Lys Glu Ala Tyr Met Ala Leu Cys Phe Leu Leu Ser Cys Arg
    35      40      45
20  agg tgt gag ata caa tca ttt gcc tct gac ttt gag ggt tgg tcc   189
    Arg Cys Glu Ile Gln Ser Phe Ala Ser Asp Phe Glu Gly Trp Ser
    50      55      60
25  tagcatgccc ctgaccagta gcccttaaa tacttcattg atatggaagg tctctgaatc 249
    ttcgtgggct taatctacca ctctctgaag ttcttatgtc tttcaaaggc ctctaaaatc 309
    tctgccatgt cttgctcacc cagttgttag catgatgtca ttgatacagt ggactttgga 369
    atctaagtgg ggagacactg gtaagtgacc aattacttca cctgtggtgt gcaagccaga 429
    tcaggaagcc tctacctgca cgacaacaca t                               460
30  VTVLWGQEAQIPMWITRRDNKNGHFTFWSPASRPKRAYMALCFLLSRRCEIQSFASDFEGWS

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35 Table 7: Alignment of various CTLA-8/IL-170 family members. The
mouse CTLA-8 sequence is SEQ ID NO: 31 (see GB L13839; 293329/30);
30 CTLA-8 is SEQ ID NO: 32 (see GB 1469917/8); human
Saimiri virus ORF13 is SEQ ID NO: 34 (see GB Y13183; 2370235).
40 CLUSTAL X (1.64b) multiple sequence alignment

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45 IL-74_Mu -----MYQAVFLAMIVGTHTVSLRI-----QEGCSHLPSCCPSKEQEPPEEWLKWWS
    IL-74_Hu -----MYQVAVFLAMVMGTHTY-----S---HWPSCCPSKQODTSEELLRWS
    IL-72_Hu -----MDWPHNLLFLLTISIFLGLGQPRSPKSKRKGQGRPGPLVPGPHQVPLDLVSRMK
    IL-72_Mu -----MDWPHSLLFLLAISIFLAPSHPRNTKGKRGQGRPSPLAPGPHQVPLDLVSRVK
    50 IL-73_Mu --MLGTLVWMLLVGFLLALAPGRAAGALRT--GRRP--ARPRDCADRPEELLEQLYGRLA
    IL-73_Hu -----MLVAGFLLALPPSWAAGAPRA--GRRP--ARPRGCADRPEELLEQLYGRLA
    IL-17_Hu --MTPGKTSLSVLLLLLSLEAIVKAGITIP-----RNPGCPNSEDKNFRTVMVNL
    IL-17_Hs --MTPRKTSLV-LLLLLSIDCIVKSETTSA-----QTPRCLAANN-SFPRSVMTL
    IL-17_Rt -----MCLMLLLLNLNLEATVKAIVLIP-----QSSVCPNAEANNFLQNVKVN
    55 IL-17_Mu -----MLLLLLSLAATVKAIAIIP-----QSSACPNTAKDFLQNVKVN
    IL-75_Hu -----MVKYLLLSILGLAFLSEAAARKIPKVGHFTFQKPESCPEVPGSMKLDIGIIN
    IL-71_Hu MTLPLGLLFLTWLHTCLAHHDPSLRGHPHSHGTPHCYSAEELPLGQAPPHLLARGAKWGO
    *
    60 IL-74_Mu S-----ASVSPP-EPLSHTHAES---CRASKD-GPLNSRAISFWYELDRDLNRV
    IL-74_Hu T-----VPVPEPL-EPAPNRRHPES---CRASED-GPLNSRAISFWRYELDRDLNRL
    IL-72_Hu P-YARMEEYERNIEEMVAQLRNSSELAQ-RKCEVNLQLWMSNKRSLSPWGYSINHDPRI
    65 IL-72_Mu P-YARMEEYERNLGEVVAQLRNSSEPAK-KKCEVNLQLWLSNKRSLSPWGYSINHDPRI
    IL-73_Mu AGVLSAFHHTLQLGPR-EQARNASCPAGGRAADRRFR-PPTNLRVSFWAYRISYDPARY
    IL-73_Hu AGVLSAFHHTLQLGPR-EQARNASCPAGGRPADDRFR-PPTNLRVSFWAYRISYDPARY
    IL-17_Hu N-----IHNRTNTN-----P-KRSSDYNRSTSPWNLHRNEDPDRI
    IL-17_Hs S-----IRNWTSS-----KRASDYNRSTSPWTLHRNEDQDRI
    IL-17_Rt K-----VINSLSKA-----SSRRPSDYLNRSTSPWTLHRNEDPDRI
    IL-17_Mu K-----VFNSLGAKV-----SSRRPSDYLNRSTSPWTLHRNEDPDRI
    70 IL-75_Hu E-----N-QRVSM-----R-NIESRSTSPWNTYTTWDPNRY
    IL-71_Hu ALPVALVSSLEAASHRGHRHERSATTCQPVLRPEEVLEADTHQRSISFWRYRVDTDEDRY
    * * *

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5      IL-74_Mu      PQDLYHARCLC PHCVSLQTGSHMDPLGNSVPLYHNQTVFYRR--PCHGEEGTHRRYCLER
      IL-74_Hu      PQDLYHARCLC PHCVSLQTGSHMDPRGNSSELLYHNQTVFYRR--PCHGEKGTHKGYCLER
      IL-72_Hu      PVDLPEARCLCLGCVNPFTM-QEDRSMVSVPVFS-QVPVRRR--LCPPPP--RTGPCRQR
15      IL-72_Mu      PADLPEARCLCLGCVNPFTM-QEDRSMVSVPVFS-QVPVRRR--LCPPPP--RPGPCRQR
      IL-73_Mu      PRYLPEAYCLCRGCLTGLYG-EEDFRFRSTPVFS-PAVVLRRTAACAG-----GRSVYA
      IL-73_Hu      PRYLPEAYCLCRGCLTGLFG-EEDVRFRSAFVYM-PTVVLRRTPACAG-----GRSVYT
      IL-17_Hu      PSVIWEAKCRHLGCINADGN--VDYHMNSVPIQQEILVLRREPPHCPN-----SFR
10      IL-17_Hs      PSVIWEAKCRYLGCVNADGN--VDYHMNSVPIQQEILVVRKGHPQPCPN-----SFR
      IL-17_Rt      PSVIWEAQRHQRVCVNAEGK--LDHMHNSVLIQQEILVLKREPEKCPF-----TFR
      IL-17_Mu      PSVIWEAQRHQRVCVNAEGK--LDHMHNSVLIQQEILVLKREPEKCPF-----TFR
      IL-75_Hu      PSEVVQAQRNLGCINAQGR--EDISMNSVPIQQETLVVRKRHQGCSV-----SFQ
      IL-71_Hu      PQKLAFACLCRGCIDARTG-RSTAALNSVRLQLSLLVLRRRRQPCSRDGSGLPTPGAFAFH
      * : * * * :
25      IL-74_Mu      RLYR-VSLACVCVRPRVMA-----
      IL-74_Hu      RLYR-VSLACVCVRPRVMG-----
      IL-72_Hu      AVMETIAGVCTCIF-----
      IL-72_Mu      VVMETIAGVCTCIF-----
20      IL-73_Mu      EHYITIPVGCTCVPEPKSADSANSSMDK----LLLGPADRPAGR
      IL-73_Hu      EAYVTIPVGCTCVPEPEKDADSINSSIDKQGAKLLGPNDA PAGP
      IL-17_Hu      LEKILVSVGCTCVTPIVHHVA-----
      IL-17_Hs      LEKMLVTVGCTCVTPIVHNV-----
20      IL-17_Rt      VEKMLVGVGCTCVSSIVRHAS-----
      IL-17_Mu      VEKMLVGVGCTCVASIVRQAA-----
25      IL-75_Hu      LEKVLVTVGCTCVTPVIHHVQ-----
      IL-71_Hu      TEFIHVPVGCTCVLPRSV-----
      : : * . * :

```

25 30 Particularly interesting segments include, e.g., those corresponding to the segments of IL-172 or IL-175, indicated above, with the other family members.

35 30 Purified protein or polypeptides are useful for generating antibodies by standard methods, as described above. Synthetic peptides or purified protein can be presented to an immune system to generate a specific binding composition, e.g., monoclonal or polyclonal antibodies. See, e.g., Coligan (1991)

35 40 Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press.

40 45 For example, the specific binding composition could be used for screening of an expression library made from a cell line which expresses an IL-170 protein. The screening can be standard staining of surface expressed protein, or by panning. Screening of intracellular expression can also be performed by various staining or immunofluorescence procedures. The binding compositions could be used to affinity purify or sort out cells

45 50 expressing the protein.

50 This invention contemplates use of isolated DNA or fragments to encode a biologically active corresponding IL-170 protein or polypeptide. In addition, this invention covers

5 isolated or recombinant DNA which encodes a biologically active
protein or polypeptide and which is capable of hybridizing
under appropriate conditions with the DNA sequences described
herein. Said biologically active protein or polypeptide can be
10 5 an intact antigen, or fragment, and have an amino acid sequence
as disclosed in Tables 1-6. Further, this invention covers the
use of isolated or recombinant DNA, or fragments thereof, which
encode proteins which are homologous to an IL-170 protein or
15 which were isolated using cDNA encoding an IL-170 protein as a
20 10 probe. The isolated DNA can have the respective regulatory
sequences in the 5' and 3' flanks, e.g., promoters, enhancers,
poly-A addition signals, and others.

20 An "isolated" nucleic acid is a nucleic acid, e.g., an
15 RNA, DNA, or a mixed polymer, which is substantially separated
from other components which naturally accompany a native
sequence, e.g., ribosomes, polymerases, and flanking genomic
sequences from the originating species. The term embraces a
25 20 nucleic acid sequence which has been removed from its naturally
occurring environment, and includes recombinant or cloned DNA
isolates and chemically synthesized analogs or analogs
30 biologically synthesized by heterologous systems. A
substantially pure molecule includes isolated forms of the
molecule. Alternatively, a purified species may be separated
35 25 from host components from a recombinant expression system. The
size of homology of such a nucleic acid will typically be less
than large vectors, e.g., less than tens of kB, typically less
than several kB, and preferably in the 2-6 kB range.

40 An isolated nucleic acid will generally be a homogeneous
30 composition of molecules, but will, in some embodiments,
contain minor heterogeneity. This heterogeneity is typically
found at the polymer ends or portions not critical to a desired
biological function or activity.

45 A "recombinant" nucleic acid is defined either by its
35 method of production or its structure. In reference to its
method of production, e.g., a product made by a process, the
process is use of recombinant nucleic acid techniques, e.g.,
50 involving human intervention in the nucleotide sequence,
typically selection or production. Alternatively, it can be a

5 nucleic acid made by generating a sequence comprising fusion of
two fragments which are not naturally contiguous to each other,
but is meant to exclude products of nature, e.g., naturally
occurring mutants. Thus, for example, products made by
10 5 transforming cells with any unnaturally occurring vector is
encompassed, as are nucleic acids comprising sequence derived
using any synthetic oligonucleotide process. Such is often
done to replace a codon with a redundant codon encoding the
15 same or a conservative amino acid, while typically introducing
or removing a sequence recognition site. Alternatively, it is
performed to join together nucleic acid segments of desired
functions to generate a single genetic entity comprising a
20 desired combination of functions not found in the commonly
available natural forms. Restriction enzyme recognition sites
15 are often the target of such artificial manipulations, but
other site specific targets, e.g., promoters, DNA replication
sites, regulation sequences, control sequences, or other useful
25 features may be incorporated by design. A similar concept is
intended for a recombinant, e.g., fusion, polypeptide.
20 Specifically included are synthetic nucleic acids which, by
genetic code redundancy, encode polypeptides similar to
30 fragments of these antigens, and fusions of sequences from
various different species variants.

A significant "fragment" in a nucleic acid context is a
25 contiguous segment of at least about 17 nucleotides, generally
35 at least 20 nucleotides, more generally at least 23
nucleotides, ordinarily at least 26 nucleotides, more
ordinarily at least 29 nucleotides, often at least 32
nucleotides, more often at least 35 nucleotides, typically at
40 30 least 38 nucleotides, more typically at least 41 nucleotides,
usually at least 44 nucleotides, more usually at least 47
nucleotides, preferably at least 50 nucleotides, more
preferably at least 53 nucleotides, and in particularly
45 preferred embodiments will be at least 56 or more nucleotides.
35 Said fragments may have termini at any location, but especially
at boundaries between structural domains.

In other embodiments, the invention provides
50 polynucleotides (or polypeptides) which comprise a plurality of
distinct, e.g., nonoverlapping, segments of the specified

length. Typically, the plurality will be at least two, more usually at least three, and preferably 5, 7, or even more. While the length minima are provided, longer lengths, of various sizes, may be appropriate, e.g., one of length 7, and two of length 12.

A DNA which codes for an IL-170 protein will be particularly useful to identify genes, mRNA, and cDNA species which code for related or homologous proteins, as well as DNAs which code for homologous proteins from different species.

There are likely homologues in other species, including primates. Various CTLA-8 proteins should be homologous and are encompassed herein. However, even proteins that have a more distant evolutionary relationship to the antigen can readily be isolated under appropriate conditions using these sequences if they are sufficiently homologous. Primate CTLA-8 protein proteins are of particular interest.

This invention further covers recombinant DNA molecules and fragments having a DNA sequence identical to or highly homologous to the isolated DNAs set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. Alternatively, recombinant clones derived from the genomic sequences, e.g., containing introns, will be useful for transgenic studies, including, e.g., transgenic cells and organisms, and for gene therapy. See, e.g., Goodnow (1992) "Transgenic Animals" in Roitt (ed.) Encyclopedia of Immunology Academic Press, San Diego, pp. 1502-1504; Travis (1992) Science 256:1392-1394; Kuhn, et al. (1991) Science 254:707-710; Capecchi (1989) Science 244:1288; Robertson (ed. 1987) Teratocarcinomas and Embryonic Stem Cells: A Practical Approach IRL Press, Oxford; Rosenberg (1992) J. Clinical Oncology 10:180-199; and Cournoyer and Caskey (1993) Ann. Rev. Immunol. 11:297-329.

Homologous nucleic acid sequences, when compared, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. The hybridization conditions are described in greater detail below.

Substantial homology in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 50% of the nucleotides, generally at least 56%, more generally at least 59%, ordinarily at least 62%, more ordinarily at least 65%, often at least 68%, more often at least 71%, typically at least 74%, more typically at least 77%, usually at least 80%, more usually at least about 85%, preferably at least about 90%, more preferably at least about 95 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides. Alternatively, substantial homology exists when the segments will hybridize under selective hybridization conditions, to a strand, or its complement, typically using a sequence derived from Table 2, 3, or 6. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, preferably at least about 65%, more preferably at least about 75%, and most preferably at least about 90%.

See, Kanehisa (1984) Nuc. Acids Res. 12:203-213. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, usually at least about 20 nucleotides, more usually at least about 24 nucleotides, typically at least about 28 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters, typically those controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 1000 mM, usually less than about 500 mM, more usually less than

5 about 400 mM, typically less than about 300 mM, preferably less than about 200 mM, and more preferably less than about 150 mM. However, the combination of parameters is much more important than the measure of any single parameter. See, e.g., Wetmur
10 and Davidson (1968) J. Mol. Biol. 31:349-370. Hybridization under stringent conditions should give a background of at least 2-fold over background, preferably at least 3-5 or more.

15 Alternatively, for sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test
20 and reference sequences are input into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. The sequence comparison algorithm then calculates the percent sequence
25 identity for the test sequence(s) relative to the reference sequence, based on the designated program parameters.

30 Optical alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1981) Adv. Appl. Math. 2:482, by the homology
35 alignment algorithm of Needleman and Wunsch (1970) J. Mol. Biol. 48:443, by the search for similarity method of Pearson and Lipman (1988) Proc. Nat'l Acad. Sci. USA 85:2444, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package,
40 Genetics Computer Group, 575 Science Dr., Madison, WI), or by visual inspection (see generally Ausubel, et al., supra).

45 One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show
50 relationship and percent sequence identity. It also plots a tree or dendrogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle (1987) J. Mol. Evol. 35:351-360. The method used is similar to the
55 method described by Higgins and Sharp (1989) CABIOS 5:151-153. The program can align up to 300 sequences, each of a maximum length of 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned

5 sequences. This cluster is then aligned to the next most
related sequence or cluster of aligned sequences. Two clusters
of sequences are aligned by a simple extension of the pairwise
alignment of two individual sequences. The final alignment is
10 5 achieved by a series of progressive, pairwise alignments. The
program is run by designating specific sequences and their
amino acid or nucleotide coordinates for regions of sequence
comparison and by designating the program parameters. For
15 example, a reference sequence can be compared to other test
20 sequences to determine the percent sequence identity
relationship using the following parameters: default gap weight
(3.00), default gap length weight (0.10), and weighted end
gaps.

Another example of algorithm that is suitable for
15 determining percent sequence identity and sequence similarity
is the BLAST algorithm, which is described Altschul, et al.
(1990) J. Mol. Biol. 215:403-410. Software for performing
25 BLAST analyses is publicly available through the National
Center for Biotechnology Information
20 (<http://www.ncbi.nlm.nih.gov/>). This algorithm involves first
identifying high scoring sequence pairs (HSPs) by identifying
30 short words of length W in the query sequence, which either
match or satisfy some positive-valued threshold score T when
aligned with a word of the same length in a database sequence.
25 T is referred to as the neighborhood word score threshold
35 (Altschul, et al., supra). These initial neighborhood word
hits act as seeds for initiating searches to find longer HSPs
containing them. The word hits are then extended in both
directions along each sequence for as far as the cumulative
40 alignment score can be increased. Extension of the word hits
in each direction are halted when: the cumulative alignment
score falls off by the quantity X from its maximum achieved
value; the cumulative score goes to zero or below, due to the
45 accumulation of one or more negative-scoring residue
35 alignments; or the end of either sequence is reached. The
BLAST algorithm parameters W, T, and X determine the
sensitivity and speed of the alignment. The BLAST program uses
50 as defaults a wordlength (W) of 11, the BLOSUM62 scoring matrix
(see Henikoff and Henikoff (1989) Proc. Nat'l Acad. Sci. USA

89:10915) alignments (B) of 50, expectation (E) of 10, M=5, N=4, and a comparison of both strands.

In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul (1993) Proc. Nat'l Acad. Sci. USA 90:5873-5787). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.1, more preferably less than about 0.01, and most preferably less than about 0.001.

A further indication that two nucleic acid sequences of polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules hybridize to each other under stringent conditions, as described below.

CTLA-8-like proteins from other mammalian species can be cloned and isolated by cross-species hybridization of closely related species, e.g., human, as disclosed in Tables 1-7.

Homology may be relatively low between distantly related species, and thus hybridization of relatively closely related species is advisable. Alternatively, preparation of an antibody preparation which exhibits less species specificity may be useful in expression cloning approaches.

III. Purified IL-170 protein

The predicted sequence of primate, e.g., human, and rodent, e.g., mouse, IL-173 polypeptide sequence is shown in Table 2. Similarly, in Table 3, is provided primate, e.g.,

human, IL-174 sequence, and is assigned SEQ ID NO: 14. A rodent, e.g., murine, IL-174 is also described in Table 3. The peptide sequences allow preparation of peptides to generate antibodies to recognize such segments.

As used herein, the terms "primate IL-170 protein" and "rodent IL-170 protein" shall encompass, when used in a protein context, a protein having designated amino acid sequences shown in Tables 1-7, or a significant fragment of such a protein. It also refers to a primate or rodent derived polypeptide which exhibits similar biological function or interacts with IL-170 protein specific binding components. These binding components, e.g., antibodies, typically bind to an IL-170 protein with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. Homologous proteins would be found in mammalian species other than rat or humans, e.g., mouse, primates, and in the herpes virus genome, e.g., ORF13. Non-mammalian species should also possess structurally or functionally related genes and proteins.

The term "polypeptide" as used herein includes a significant fragment or segment, and encompasses a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. The specific ends of such a segment will be at any combinations within the protein, preferably encompassing structural domains.

The term "binding composition" refers to molecules that bind with specificity to IL-170 protein, e.g., in a ligand-receptor type fashion, an antibody-antigen interaction, or compounds, e.g., proteins which specifically associate with IL-170 protein, e.g., in a natural physiologically relevant protein-protein interaction, either covalent or non-covalent. The molecule may be a polymer, or chemical reagent. No

5 implication as to whether IL-170 protein is either the ligand
or the receptor of a ligand-receptor interaction is
represented, other than the interaction exhibit similar
specificity, e.g., specific affinity. A functional analog may
10 be a protein with structural modifications, or may be a wholly
unrelated molecule, e.g., which has a molecular shape which
interacts with the appropriate binding determinants. The
proteins may serve as agonists or antagonists of a receptor,
see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The
15 Pharmacological Bases of Therapeutics (8th ed.), Pergamon
20 Press.

Solubility of a polypeptide or fragment depends upon the
environment and the polypeptide. Many parameters affect
20 polypeptide solubility, including temperature, electrolyte
15 environment, size and molecular characteristics of the
polypeptide, and nature of the solvent. Typically, the
temperature at which the polypeptide is used ranges from about
25 4° C to about 65° C. Usually the temperature at use is greater
than about 18° C and more usually greater than about 22° C.
20 For diagnostic purposes, the temperature will usually be about
room temperature or warmer, but less than the denaturation
30 temperature of components in the assay. For therapeutic
purposes, the temperature will usually be body temperature,
typically about 37° C for humans, though under certain
25 situations the temperature may be raised or lowered in situ or
in vitro.

The electrolytes will usually approximate in situ
physiological conditions, but may be modified to higher or
lower ionic strength where advantageous. The actual ions may
40 be modified, e.g., to conform to standard buffers used in
30 physiological or analytical contexts.

The size and structure of the polypeptide should generally
be in a substantially stable state, and usually not in a
45 denatured state. The polypeptide may be associated with other
35 polypeptides in a quaternary structure, e.g., to confer
solubility, or associated with lipids or detergents in a manner
which approximates natural lipid bilayer interactions.

50 The solvent will usually be a biologically compatible
buffer, of a type used for preservation of biological

activities, and will usually approximate a physiological solvent. Usually the solvent will have a neutral pH, typically between about 5 and 10, and preferably about 7.5. On some occasions, a detergent will be added, typically a mild non-denaturing one, e.g., CHS or CHAPS, or a low enough concentration as to avoid significant disruption of structural or physiological properties of the antigen.

Solubility is reflected by sedimentation measured in Svedberg units, which are a measure of the sedimentation velocity of a molecule under particular conditions. The determination of the sedimentation velocity was classically performed in an analytical ultracentrifuge, but is typically now performed in a standard ultracentrifuge. See, Freifelder (1982) Physical Biochemistry (2d ed.), W.H. Freeman; and Cantor and Schimmel (1980) Biophysical Chemistry, parts 1-3, W.H. Freeman & Co., San Francisco. As a crude determination, a sample containing a putatively soluble polypeptide is spun in a standard full sized ultracentrifuge at about 50K rpm for about 10 minutes, and soluble molecules will remain in the supernatant. A soluble particle or polypeptide will typically be less than about 30S, more typically less than about 15S, usually less than about 10S, more usually less than about 6S, and, in particular embodiments, preferably less than about 4S, and more preferably less than about 3S.

IV. Making IL-170 protein; Mimetics

DNA which encodes the IL-170 protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length protein or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding studies; for construction and expression of modified molecules; and for structure/function studies. Each antigen or its fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These molecules can be substantially purified to be free of protein or cellular

contaminants, other than those derived from the recombinant host, and therefore are particularly useful in pharmaceutical compositions when combined with a pharmaceutically acceptable carrier and/or diluent. The antigen, or portions thereof, may be expressed as fusions with other proteins.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired antigen gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell. Methods for amplifying vector copy number are also known, see, e.g., Kaufman, et al. (1985) Molec. and Cell. Biol. 5:1750-1759.

The vectors of this invention contain DNA which encodes an IL-170 protein, or a fragment thereof, typically encoding a biologically active polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNA coding for an IL-170 protein in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNA coding for the antigen is inserted into the vector such that growth of the host containing the vector expresses the cDNA in question. Usually, expression vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector replicate in a host cell,

5 e.g., it is possible to effect transient expression of th
antigen or its fragments in various hosts using vectors that do
not contain a replication origin that is recognized by the host
cell. It is also possible to use vectors that cause
10 5 integration of an IL-170 protein gene or its fragments into the
host DNA by recombination, or to integrate a promoter which
controls expression of an endogenous gene.

15 Vectors, as used herein, comprise plasmids, viruses,
bacteriophage, integratable DNA fragments, and other vehicles
10 which enable the integration of DNA fragments into the genome
of the host. Expression vectors are specialized vectors which
contain genetic control elements that effect expression of
operably linked genes. Plasmids are the most commonly used
20 form of vector but all other forms of vectors which serve an
equivalent function and which are, or become, known in the art
15 are suitable for use herein. See, e.g., Pouwels, et al. (1985
and Supplements) Cloning Vectors: A Laboratory Manual,
Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A
25 Survey of Molecular Cloning Vectors and Their Uses,
Buttersworth, Boston, MA.

30 Transformed cells include cells, preferably mammalian,
that have been transformed or transfected with vectors
containing an IL-170 gene, typically constructed using
recombinant DNA techniques. Transformed host cells usually
25 express the antigen or its fragments, but for purposes of
cloning, amplifying, and manipulating its DNA, do not need to
35 express the protein. This invention further contemplates
culturing transformed cells in a nutrient medium, thus
permitting the protein to accumulate in the culture. The
40 30 protein can be recovered, either from the culture or from the
culture medium.

45 For purposes of this invention, DNA sequences are operably
linked when they are functionally related to each other. For
example, DNA for a presequence or secretory leader is operably
35 linked to a polypeptide if it is expressed as a preprotein or
participates in directing the polypeptide to the cell membrane
or in secretion of the polypeptide. A promoter is operably
50 linked to a coding sequence if it controls the transcription of
the polypeptide; a ribosome binding site is operably linked to

5 a coding sequence if it is positioned to permit translation.
Usually, operably linked means contiguous and in reading frame,
however, certain genetic elements such as repressor genes are
not contiguously linked but still bind to operator sequences
10 5 that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes,
and higher eukaryotes. Prokaryotes include both gram negative
and gram positive organisms, e.g., *E. coli* and *B. subtilis*.
15 Lower eukaryotes include yeasts, e.g., *S. cerevisiae* and
20 *Pichia*, and species of the genus *Dictyostelium*. Higher
eukaryotes include established tissue culture cell lines from
animal cells, both of non-mammalian origin, e.g., insect cells,
and birds, and of mammalian origin, e.g., human, primates, and
rodents.

15 Prokaryotic host-vector systems include a wide variety of
vectors for many different species. As used herein, *E. coli*
and its vectors will be used generically to include equivalent
25 vectors used in other prokaryotes. A representative vector for
amplifying DNA is pBR322 or many of its derivatives. Vectors
20 that can be used to express the IL-170 proteins or its
fragments include, but are not limited to, such vectors as
those containing the lac promoter (pUC-series); trp promoter
(pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR
promoters (pOTS); or hybrid promoters such as ptac (pDR540).
30 See Brosius, et al. (1988) "Expression Vectors Employing
Lambda-, trp-, lac-, and Ipp-derived Promoters", in Rodriguez
and Denhardt (eds.) Vectors: A Survey of Molecular Cloning
35 Vectors and Their Uses, Butterworth, Boston, Chapter 10, pp.
205-236.

40 30 Lower eukaryotes, e.g., yeasts and *Dictyostelium*, may be
transformed with vectors encoding IL-170 proteins. For
purposes of this invention, the most common lower eukaryotic
host is the baker's yeast, *Saccharomyces cerevisiae*. It will
45 be used to generically represent lower eukaryotes although a
35 number of other strains and species are also available. Yeast
vectors typically consist of a replication origin (unless of
the integrating type), a selection gene, a promoter, DNA
50 encoding the desired protein or its fragments, and sequences
for translation termination, polyadenylation, and transcription

5 termination. Suitable expression vectors for yeast include
such constitutive promoters as 3-phosphoglycerate kinase and
various other glycolytic enzyme gene promoters or such
10 inducible promoters as the alcohol dehydrogenase 2 promoter or
5 metallothionine promoter. Suitable vectors include derivatives
of the following types: self-replicating low copy number (such
as the YRp-series), self-replicating high copy number (such as
the YEp-series); integrating types (such as the YIp-series), or
15 mini-chromosomes (such as the YCp-series).

20 Higher eukaryotic tissue culture cells are the preferred
host cells for expression of the functionally active IL-170
protein. In principle, many higher eukaryotic tissue culture
cell lines are workable, e.g., insect baculovirus expression
25 systems, whether from an invertebrate or vertebrate source.
However, mammalian cells are preferred, in that the processing,
both cotranslationally and posttranslationally. Transformation
or transfection and propagation of such cells has become a
routine procedure. Examples of useful cell lines include HeLa
30 cells, Chinese hamster ovary (CHO) cell lines, baby rat kidney
(BRK) cell lines, insect cell lines, bird cell lines, and
monkey (COS) cell lines. Expression vectors for such cell
lines usually include an origin of replication, a promoter, a
translation initiation site, RNA splice sites (if genomic DNA
is used), a polyadenylation site, and a transcription
35 termination site. These vectors also usually contain a
selection gene or amplification gene. Suitable expression
vectors may be plasmids, viruses, or retroviruses carrying
promoters derived, e.g., from such sources as from adenovirus,
SV40, parvoviruses, vaccinia virus, or cytomegalovirus.

40 Representative examples of suitable expression vectors include
pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-
1142; pMC1neo Poly-A, see Thomas, et al. (1987) Cell 51:503-
512; and a baculovirus vector such as pAC 373 or pAC 610, see
45 O'Reilly, et al. (1992) Baculovirus Expression Vectors: A
35 Laboratory Manual Freeman and Co., CRC Press, Boca Raton, Fla.

It will often be desired to express an IL-170 protein
50 polypeptide in a system which provides a specific or defined
glycosylation pattern. In this case, the usual pattern will be
that provided naturally by the expression system. However, the

5 pattern will be modifiable by exposing the polypeptide, e.g.,
an unglycosylated form, to appropriate glycosylating proteins
introduced into a heterologous expression system. For example,
the IL-170 protein gene may be co-transformed with one or more
10 5 genes encoding mammalian or other glycosylating enzymes. Using
this approach, certain mammalian glycosylation patterns will be
achievable or approximated in prokaryote or other cells.

15 The IL-170 protein, or a fragment thereof, may be
engineered to be phosphatidyl inositol (PI) linked to a cell
20 10 membrane, but can be removed from membranes by treatment with a
phosphatidyl inositol cleaving enzyme, e.g., phosphatidyl
inositol phospholipase-C. This releases the antigen in a
biologically active form, and allows purification by standard
20 procedures of protein chemistry. See, e.g., Low (1989)
15 Biochim. Biophys. Acta 988:427-454; Tse, et al. (1985) Science
230:1003-1008; and Brunner, et al. (1991) J. Cell Biol.
114:1275-1283.

25 Now that the IL-170 protein has been characterized,
fragments or derivatives thereof can be prepared by
20 conventional processes for synthesizing peptides. These
include processes such as are described in Stewart and Young
30 (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co.,
Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of
Peptide Synthesis, Springer-Verlag, New York; and Bodanszky
25 (1984) The Principles of Peptide Synthesis, Springer-Verlag,
New York. For example, an azide process, an acid chloride
35 process, an acid anhydride process, a mixed anhydride process,
an active ester process (for example, p-nitrophenyl ester, N-
hydroxysuccinimide ester, or cyanomethyl ester), a
40 30 carbodiimidazole process, an oxidative-reductive process, or a
dicyclohexylcarbodiimide (DCCD)/additive process can be used.
Solid phase and solution phase syntheses are both applicable to
the foregoing processes.

45 The IL-170 protein, fragments, or derivatives are suitably
35 prepared in accordance with the above processes as typically
employed in peptide synthesis, generally either by a so-called
stepwise process which comprises condensing an amino acid to
50 the terminal amino acid, one by one in sequence, or by coupling
peptide fragments to the terminal amino acid. Amino groups

5 that are not being used in the coupling reaction are typically protected to prevent coupling at an incorrect location.

10 If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-
15 alkyloxycarbonyl-hydrazidated resins, and the like.

20 An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156.

25 The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis and various forms of chromatography, and the like. The IL-170 proteins of this invention can be obtained in varying degrees of purity depending upon its desired use.
30 Purification can be accomplished by use of the protein purification techniques disclosed herein or by the use of the antibodies herein described in immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate source cells, lysates of other cells expressing the protein, or lysates or supernatants of cells producing the IL-170 protein as a result of DNA techniques, see below.

35

V. Physical Variants

50 This invention also encompasses proteins or peptides having substantial amino acid sequence homology with the amino

55

5 acid sequence of the IL-170 protein. The variants include species or allelic variants.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches, if necessary, by
10 5 introducing gaps as required. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine;
15 10 serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are typically intended to include natural allelic and interspecies variations in each respective protein sequence. Typical homologous proteins or peptides will have from 25-100% homology (if gaps
20 15 can be introduced), to 50-100% homology (if conservative substitutions are included) with the amino acid sequence of the IL-170 protein. Homology measures will be at least about 35%, generally at least 40%, more generally at least 45%, often at least 50%, more often at least 55%, typically at least 60%,
25 20 more typically at least 65%, usually at least 70%, more usually at least 75%, preferably at least 80%, and more preferably at least 80%, and in particularly preferred embodiments, at least 85% or more. See also Needleham, et al. (1970) J. Mol. Biol. 48:443-453; Sankoff, et al. (1983) Chapter One in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison Addison-Wesley, Reading, MA; and software
30 25 packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group, Madison, WI.

The isolated DNA encoding an IL-170 protein can be readily
40 30 modified by nucleotide substitutions, nucleotide deletions, nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode these antigens, their derivatives, or proteins having similar physiological, immunogenic, or antigenic activity. These
45 35 modified sequences can be used to produce mutant antigens or to enhance expression. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant IL-170 protein derivatives
50 include predetermined or site-specific mutations of the

5 respective protein or its fragments. "Mutant IL-170 protein"
encompasses a polypeptide otherwise falling within the homology
definition of the murine IL-170 or human IL-170 protein as set
forth above, but having an amino acid sequence which differs
10 5 from that of IL-170 protein as found in nature, whether by way
of deletion, substitution, or insertion. In particular, "site
specific mutant IL-170 protein" generally includes proteins
having significant homology with the corresponding protein
15 10 having sequences from Tables 1-6, and as sharing various
biological activities, e.g., antigenic or immunogenic, with
those sequences, and in preferred embodiments contain most of
the disclosed sequences. Similar concepts apply to different
20 15 IL-170 proteins, particularly those found in various warm
blooded animals, e.g., mammals and birds. As stated before, it
is emphasized that descriptions are generally meant to
encompass all IL-170 proteins, not limited to the mouse
embodiment specifically discussed.

25 Although site specific mutation sites are predetermined,
mutants need not be site specific. IL-170 protein mutagenesis
20 20 can be conducted by making amino acid insertions or deletions.
Substitutions, deletions, insertions, or any combinations may
30 30 be generated to arrive at a final construct. Insertions
include amino- or carboxy- terminal fusions. Random
mutagenesis can be conducted at a target codon and the
25 35 expressed mutants can then be screened for the desired
activity. Methods for making substitution mutations at
predetermined sites in DNA having a known sequence are well
known in the art, e.g., by M13 primer mutagenesis or polymerase
chain reaction (PCR) techniques. See also Sambrook, et al.
40 40 (1989) and Ausubel, et al. (1987 and Supplements).

45 The mutations in the DNA normally should not place coding
sequences out of reading frames and preferably will not create
complementary regions that could hybridize to produce secondary
mRNA structure such as loops or hairpins.

50 35 The present invention also provides recombinant proteins,
e.g., heterologous fusion proteins using segments from these
proteins. A heterologous fusion protein is a fusion of
50 50 proteins or segments which are naturally not normally fused in
the same manner. Thus, the fusion product of an immunoglobulin

5 with an IL-170 polypeptide is a continuous protein molecule
having sequences fused in a typical peptide linkage, typically
made as a single translation product and exhibiting properties
derived from each source peptide. A similar concept applies to
10 5 heterologous nucleic acid sequences.

In addition, new constructs may be made from combining
similar functional domains from other proteins. For example,
antigen-binding or other segments may be "swapped" between
different new fusion polypeptides or fragments. See, e.g.,
15 10 Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et
al. (1988) J. Biol. Chem. 263:15985-15992. Thus, new chimeric
polypeptides exhibiting new combinations of specificities will
result from the functional linkage of biologically relevant
20 domains and other functional domains.

15 The phosphoramidite method described by Beaucage and
Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce
suitable synthetic DNA fragments. A double stranded fragment
25 will often be obtained either by synthesizing the complementary
strand and annealing the strand together under appropriate
20 conditions or by adding the complementary strand using DNA
polymerase with an appropriate primer sequence, e.g., PCR
30 techniques.

VI. Functional Variants

25 The blocking of physiological response to IL-170 proteins
35 may result from the inhibition of binding of the antigen to its
natural binding partner, e.g., through competitive inhibition.
Thus, in vitro assays of the present invention will often use
isolated protein, membranes from cells expressing a recombinant
40 30 membrane associated IL-170 protein, soluble fragments
comprising binding segments, or fragments attached to solid
phase substrates. These assays will also allow for the
diagnostic determination of the effects of either binding
45 segment mutations and modifications, or protein mutations and
35 modifications, e.g., analogs.

This invention also contemplates the use of competitive
drug screening assays, e.g., where neutralizing antibodies to
50 antigen or binding partner fragments compete with a test
compound for binding to the protein. In this manner, the

antibodies can be used to detect the presence of any polypeptide which shares one or more antigenic binding sites of the protein and can also be used to occupy binding sites on the protein that might otherwise interact with a binding partner.

Additionally, neutralizing antibodies against the IL-170 protein and soluble fragments of the antigen which contain a high affinity receptor binding site, can be used to inhibit antigen function in tissues, e.g., tissues experiencing abnormal physiology.

"Derivatives" of the IL-170 antigens include amino acid sequence mutants, glycosylation variants, and covalent or aggregate conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the IL-170 amino acid side chains or at the N- or C- termini, by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species. Covalent attachment to carrier proteins may be important when immunogenic moieties are haptens.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the IL-170 protein or fragments thereof with other proteins or

5 polypeptides. These derivatives can be synthesized in
recombinant culture such as N- or C-terminal fusions or by the
use of agents known in the art for their usefulness in cross-
linking proteins through reactive side groups. Preferred
10 5 antigen derivatization sites with cross-linking agents are at
free amino groups, carbohydrate moieties, and cysteine
residues.

Fusion polypeptides between the IL-170 proteins and other
homologous or heterologous proteins are also provided.

15 10 Homologous polypeptides may be fusions between different
surface markers, resulting in, e.g., a hybrid protein
exhibiting receptor binding specificity. Likewise,
heterologous fusions may be constructed which would exhibit a
20 combination of properties or activities of the derivative
proteins. Typical examples are fusions of a reporter
polypeptide, e.g., luciferase, with a segment or domain of an
antigen, e.g., a receptor-binding segment, so that the presence
25 or location of the fused antigen may be easily determined.
See, e.g., Dull, et al., U.S. Patent No. 4,859,609. Other gene
20 fusion partners include bacterial β -galactosidase, trpE,
Protein A, β -lactamase, alpha amylase, alcohol dehydrogenase,
30 and yeast alpha mating factor. See, e.g., Godowski, et al.
(1988) Science 241:812-816.

The phosphoramidite method described by Beaucage and
25 Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce
suitable synthetic DNA fragments. A double stranded fragment
will often be obtained either by synthesizing the complementary
strand and annealing the strand together under appropriate
conditions or by adding the complementary strand using DNA
40 30 polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which
have been chemically modified by phosphorylation, sulfonation,
biotinylation, or the addition or removal of other moieties,
45 particularly those which have molecular shapes similar to
35 phosphate groups. In some embodiments, the modifications will
be useful labeling reagents, or serve as purification targets,
e.g., affinity ligands.

50 Fusion proteins will typically be made by either
recombinant nucleic acid methods or by synthetic polypeptide

5 methods. Techniques for nucleic acid manipulation and
expression are described generally, for example, in Sambrook,
et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.),
10 Vols. 1-3, Cold Spring Harbor Laboratory. Techniques for
5 synthesis of polypeptides are described, for example, in
Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield
(1986) Science 232: 341-347; and Atherton, et al. (1989) Solid
Phase Peptide Synthesis: A Practical Approach, IRL Press,
15 Oxford.

10 This invention also contemplates the use of derivatives of
the IL-170 proteins other than variations in amino acid
sequence or glycosylation. Such derivatives may involve
20 covalent or aggregative association with chemical moieties.
These derivatives generally fall into the three classes: (1)
15 salts, (2) side chain and terminal residue covalent
modifications, and (3) adsorption complexes, for example with
cell membranes. Such covalent or aggregative derivatives are
25 useful as immunogens, as reagents in immunoassays, or in
purification methods such as for affinity purification of
20 antigens or other binding proteins. For example, an IL-170
antigen can be immobilized by covalent bonding to a solid
support such as cyanogen bromide-activated Sepharose, by
30 methods which are well known in the art, or adsorbed onto
polyolefin surfaces, with or without glutaraldehyde cross-
25 linking, for use in the assay or purification of anti-IL-170
protein antibodies or its receptor or other binding partner.
The IL-170 antigens can also be labeled with a detectable
group, for example radioiodinated by the chloramine T
40 procedure, covalently bound to rare earth chelates, or
30 conjugated to another fluorescent moiety for use in diagnostic
assays. Purification of IL-170 protein may be effected by
immobilized antibodies or binding partners.

45 A solubilized IL-170 antigen or fragment of this invention
can be used as an immunogen for the production of antisera or
35 antibodies specific for the protein or fragments thereof. The
purified antigen can be used to screen monoclonal antibodies or
binding fragments prepared by immunization with various forms
50 of impure preparations containing the protein. In particular,
the term "antibodies" also encompasses antigen binding

5 fragments of natural antibodies. The purified IL-170 proteins
can also be used as a reagent to detect any antibodies
generated in response to the presence of elevated levels of the
protein or cell fragments containing the antigen, both of which
10 5 may be diagnostic of an abnormal or specific physiological or
disease condition. Additionally, antigen fragments may also
serve as immunogens to produce the antibodies of the present
invention, as described immediately below. For example, this
15 invention contemplates antibodies raised against amino acid
10 sequences encoded by nucleotide sequences shown in Tables 1-6,
or fragments of proteins containing them. In particular, this
invention contemplates antibodies having binding affinity to or
20 being raised against specific fragments which are predicted to
lie outside of the lipid bilayer.

15 The present invention contemplates the isolation of
additional closely related species variants. Southern blot
analysis established that similar genetic entities exist in
25 other mammals, e.g., rat and human. It is likely that the IL-
170 proteins are widespread in species variants, e.g., rodents,
20 lagomorphs, carnivores, artiodactyla, perissodactyla, and
primates.

30 The invention also provides means to isolate a group of
related antigens displaying both distinctness and similarities
in structure, expression, and function. Elucidation of many of
35 25 the physiological effects of the antigens will be greatly
accelerated by the isolation and characterization of distinct
species variants. In particular, the present invention
provides useful probes for identifying additional homologous
genetic entities in different species.

40 30 The isolated genes will allow transformation of cells
lacking expression of a corresponding IL-170 protein, e.g.,
either species types or cells which lack corresponding antigens
and should exhibit negative background activity. Expression of
45 transformed genes will allow isolation of antigenically pure
35 cell lines, with defined or single specie variants. This
approach will allow for more sensitive detection and
discrimination of the physiological effects of IL-170 proteins.
50 Subcellular fragments, e.g., cytoplasts or membrane fragments,
can be isolated and used.

5 Dissection of the critical structural elements which
effect the various physiological or differentiation functions
provided by the proteins is possible using standard techniques
of modern molecular biology, particularly in comparing members
10 of the related class. See, e.g., the homolog-scanning
mutagenesis technique described in Cunningham, et al. (1989)
Science 243:1339-1336; and approaches used in O'Dowd, et al.
(1988) J. Biol. Chem. 263:15985-15992; and Lechleiter, et al.
15 (1990) EMBO J. 9:4381-4390.

20 In particular, functional domains or segments can be
substituted between species variants to determine what
structural features are important in both binding partner
affinity and specificity, as well as signal transduction. An
array of different variants will be used to screen for
15 molecules exhibiting combined properties of interaction with
different species variants of binding partners.

25 Antigen internalization may occur under certain
circumstances, and interaction between intracellular components
and "extracellular" segments of proteins involved in
20 interactions may occur. The specific segments of interaction
of IL-170 protein with other intracellular components may be
identified by mutagenesis or direct biochemical means, e.g.,
cross-linking or affinity methods. Structural analysis by
crystallographic or other physical methods will also be
30 applicable. Further investigation of the mechanism of
biological function will include study of associated components
which may be isolatable by affinity methods or by genetic
means, e.g., complementation analysis of mutants.

40 Further study of the expression and control of IL-170
30 protein will be pursued. The controlling elements associated
with the antigens may exhibit differential developmental,
tissue specific, or other expression patterns. Upstream or
downstream genetic regions, e.g., control elements, are of
45 interest.

35 Structural studies of the antigen will lead to design of
new variants, particularly analogs exhibiting agonist or
antagonist properties on binding partners. This can be
50 combined with previously described screening methods to isolate
variants exhibiting desired spectra of activities.

5 Expression in other cell types will often result in glycosylation differences in a particular antigen. Various species variants may exhibit distinct functions based upon structural differences other than amino acid sequence.

10 5 Differential modifications may be responsible for differential function, and elucidation of the effects are now made possible.

15 Thus, the present invention provides important reagents related to antigen-binding partner interaction. Although the foregoing description has focused primarily upon the murine IL-
20 170 and human IL-170 protein, those of skill in the art will immediately recognize that the invention encompasses other antigens, e.g., mouse and other mammalian species or allelic variants, as well as variants thereof.

15 VII. Antibodies

25 Antibodies can be raised to the various IL-170 proteins, including species or allelic variants, and fragments thereof, both in their naturally occurring forms and in their recombinant forms. Additionally, antibodies can be raised to
30 IL-170 proteins in either their active forms or in their inactive forms. Anti-idiotypic antibodies are also contemplated.

35 Antibodies, including binding fragments and single chain versions, against predetermined fragments of the antigens can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective
40 IL-170 proteins, or screened for agonistic or antagonistic activity, e.g., mediated through a binding partner. These monoclonal antibodies will usually bind with at least a K_D of about 1 mM, more usually at least about 300 μ M, typically at least about 10 μ M, more typically at least about 30 μ M,
45 preferably at least about 10 μ M, and more preferably at least about 3 μ M or better.

50 An IL-170 polypeptide that specifically binds to or that is specifically immunoreactive with an antibody, e.g., such as a polyclonal antibody, generated against a defined immunogen, e.g., such as an immunogen consisting of an amino acid sequence

5 of mature SEQ ID NO: 8 or fragments thereof or a polypeptide
generated from the nucleic acid of SEQ ID NO: 7 is typically
determined in an immunoassay. Included within the metes and
10 5 sequences described herein, including functional variants, that
encode polypeptides that selectively bind to polyclonal
antibodies generated against the prototypical IL-173, IL-174,
IL-176, or IL-177 polypeptide as structurally and functionally
15 10 defined herein. The immunoassay typically uses a polyclonal
antiserum which was raised, e.g., to a protein of SEQ ID NO: 8.
This antiserum is selected to have low crossreactivity against
appropriate other IL-170 family members, preferably from the
20 same species, and any such crossreactivity is removed by
immunoabsorption prior to use in the immunoassay. Appropriate
15 selective serum preparations can be isolated, and
characterized.

25 In order to produce antisera for use in an immunoassay,
the protein, e.g., of SEQ ID NO: 8, is isolated as described
herein. For example, recombinant protein may be produced in a
20 mammalian cell line. An appropriate host, e.g., an inbred
strain of mice such as Balb/c, is immunized with the protein of
30 SEQ ID NO: 8 using a standard adjuvant, such as Freund's
adjuvant, and a standard mouse immunization protocol (see
Harlow and Lane). Alternatively, a substantially full length
25 synthetic peptide derived from the sequences disclosed herein
can be used as an immunogen. Polyclonal sera are collected and
titered against the immunogen protein in an immunoassay, e.g.,
a solid phase immunoassay with the immunogen immobilized on a
40 solid support. Polyclonal antisera with a titer of 10^4 or
30 greater are selected and tested for their cross reactivity
against other IL-170 family members, e.g., IL-171, IL-172, or
IL-175, using a competitive binding immunoassay such as the one
described in Harlow and Lane, supra, at pages 570-573.
45 Preferably at least two IL-170 family members are used in this
35 determination in conjunction with the target. These IL-170
family members can be produced as recombinant proteins and
isolated using standard molecular biology and protein chemistry
50 techniques as described herein. Thus, antibody preparations

5 can be identified or produced having desired selectivity or specificity for subsets of IL-170 family members.

Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of mature SEQ ID NO: 8 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the protein of SEQ ID NO: 8. The percent crossreactivity for the above proteins is calculated, using standard calculations. Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.

The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein. In order to make this comparison, the two proteins are each assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of, e.g., SEQ ID NO: 8 that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to a binding partner and inhibit antigen binding or inhibit the ability of an antigen to elicit a biological response. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides so that when the antibody binds to the antigen, a cell expressing it, e.g., on its surface, is killed. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker, and may effect drug targeting.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they can be screened for ability to bind to the

antigens without inhibiting binding by a partner. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying IL-170 protein or its binding partners. See, e.g.,

- 5 Chan (ed. 1987) Immunoassay: A Practical Guide Academic Press, Orlando, Fla.; Ngo (ed. 1988) Nonisotopic Immunoassay Plenum Press, NY; and Price and Newman (eds. 1991) Principles and Practice of Immunoassay Stockton Press, NY.

15 Antigen fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. An antigen and its fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York, and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York, for descriptions of methods of preparing polyclonal antisera. A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

25 In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed.) Academic Press, New York; and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Summarized briefly, this method involves injecting an animal with an immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas

5 is then screened to isolate individual clones, each of which
secrete a single antibody species to the immunogen. In this
manner, the individual antibody species obtained are the
10 products of immortalized and cloned single B cells from the
5 immune animal generated in response to a specific site
recognized on the immunogenic substance.

Other suitable techniques involve in vitro exposure of
15 lymphocytes to the antigenic polypeptides or alternatively to
selection of libraries of antibodies in phage or similar
10 vectors. See, Huse, et al. (1989) "Generation of a Large
Combinatorial Library of the Immunoglobulin Repertoire in Phage
Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature
20 341:544-546. The polypeptides and antibodies of the present
invention may be used with or without modification, including
15 chimeric or humanized antibodies. Frequently, the polypeptides
and antibodies will be labeled by joining, either covalently or
25 non-covalently, a substance which provides for a detectable
signal. A wide variety of labels and conjugation techniques
are known and are reported extensively in both the scientific
20 and patent literature. Suitable labels include radionuclides,
enzymes, substrates, cofactors, inhibitors, fluorescent
30 moieties, chemiluminescent moieties, magnetic particles, and
the like. Patents, teaching the use of such labels include
U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345;
35 4,277,437; 4,275,149; and 4,366,241. Also, recombinant
immunoglobulins may be produced, see Cabilly, U.S. Patent No.
4,816,567.

The antibodies of this invention can also be used for
40 affinity chromatography in isolating the protein. Columns can
be prepared where the antibodies are linked to a solid support,
30 e.g., particles, such as agarose, Sephadex, or the like, where
a cell lysate may be passed through the column, the column
45 washed, followed by increasing concentrations of a mild
denaturant, whereby the purified IL-170 protein will be
35 released.

The antibodies may also be used to screen expression
50 libraries for particular expression products. Usually the
antibodies used in such a procedure will be labeled with a

5 moiety allowing easy detection of presence of antigen by antibody binding.

Antibodies raised against each IL-170 protein will also be useful to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various immunological conditions related to expression of the respective antigens.

VIII. Uses

15 The present invention provides reagents which will find use in diagnostic applications as described elsewhere herein, e.g., in the general description for physiological or developmental abnormalities, or below in the description of kits for diagnosis.

20 This invention also provides reagents with significant therapeutic value. The IL-170 protein (naturally occurring or recombinant), fragments thereof, and antibodies thereto, along with compounds identified as having binding affinity to IL-170 protein, should be useful in the treatment of conditions associated with abnormal physiology or development, including abnormal proliferation, e.g., cancerous conditions, or degenerative conditions. Abnormal proliferation, regeneration, degeneration, and atrophy may be modulated by appropriate therapeutic treatment using the compositions provided herein. For example, a disease or disorder associated with abnormal expression or abnormal signaling by an IL-170 antigen should be a likely target for an agonist or antagonist of the protein.

35 Other abnormal developmental conditions are known in the cell types shown to possess IL-170 antigen mRNA by Northern blot analysis. See Berkow (ed.) The Merck Manual of Diagnosis and Therapy, Merck & Co., Rahway, N.J.; and Thorn, et al. Harrison's Principles of Internal Medicine, McGraw-Hill, N.Y. These problems may be susceptible to prevention or treatment using compositions provided herein.

45 Recombinant antibodies which bind to IL-170 can be purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active or inert ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, e.g., immunogenic adjuvants, along with physiologically innocuous stabilizers and

5 excipients. These combinations can be sterile filtered and
plac d into dosage forms as by lyophilization in dosage vials
or storage in stabilized aqueous preparations. This invention
also contemplates use of antibodies or binding fragments
10 5 thereof, including forms which are not complement binding.

Screening using IL-170 for binding partners or compounds
having binding affinity to IL-170 antigen can be performed,
including isolation of associated components. Subsequent
15 10 biological assays can then be utilized to determine if the
compound has intrinsic biological activity and is therefore an
agonist or antagonist in that it blocks an activity of the
antigen. This invention further contemplates the therapeutic
20 15 use of antibodies to IL-170 protein as antagonists. This
approach should be particularly useful with other IL-170
protein species variants.

The quantities of reagents necessary for effective therapy
will depend upon many different factors, including means of
25 20 administration, target site, physiological state of the
patient, and other medicants administered. Thus, treatment
dosages should be titrated to optimize safety and efficacy.
Typically, dosages used in vitro may provide useful guidance in
30 35 the amounts useful for in situ administration of these
reagents. Animal testing of effective doses for treatment of
particular disorders will provide further predictive indication
of human dosage. Various considerations are described, e.g.,
in Gilman, et al. (eds. 1990) Goodman and Gilman's: The
Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press;
and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack
Publishing Co., Easton, Penn. Methods for administration are
40 30 discussed therein and below, e.g., for oral, intravenous,
intraperitoneal, or intramuscular administration, transdermal
diffusion, and others. See also Langer (1990) Science
249:1527-1533. Pharmaceutically acceptable carriers will
45 35 include water, saline, buffers, and other compounds described,
e.g., in the Merck Index, Merck & Co., Rahway, New Jersey.
Dosage ranges would ordinarily be expected to be in amounts
lower than 1 mM concentrations, typically less than about 10 μ M
50 55 concentrations, usually less than about 100 nM, preferably less
than about 10 pM (picomolar), and most preferably less than

5 about 1 fM (femtomolar), with an appropriate carrier. Slow release formulations, or a slow release apparatus will often be utilized for continuous administration.

10 5 IL-170 protein, fragments thereof, and antibodies to it or its fragments, antagonists, and agonists, may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered 15 in any conventional dosage formulation. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations typically comprise at least one active ingredient, as defined above, together with one or more acceptable carriers 20 thereof. Each carrier should be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous 25 and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press, Parrytown, NY; Remington's Pharmaceutical Sciences, 17th 30 ed. (1990) Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications 2d ed., Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets 2d ed., Dekker, NY; and 40 Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY. The therapy of this invention may be combined with or used in association with other therapeutic, including cytokine, reagents.

45 Both the naturally occurring and the recombinant forms of the IL-170 proteins of this invention are particularly useful 50 in kits and assay methods which are capable of screening compounds for binding activity to the proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of

5 compounds in a short period. See, e.g., Fodor, et al. (1991)
Science 251:767-773, which describes means for testing of
binding affinity by a plurality of defined polymers synthesized
on a solid substrate. The development of suitable assays can
10 5 be greatly facilitated by the availability of large amounts of
purified, soluble IL-170 protein as provided by this invention.

This invention is particularly useful for screening
compounds by using recombinant antigen in any of a variety of
15 drug screening techniques. The advantages of using a
recombinant protein in screening for specific ligands include:
(a) improved renewable source of the antigen from a specific
source; (b) potentially greater number of antigen molecules per
20 cell giving better signal to noise ratio in assays; and (c)
species variant specificity (theoretically giving greater
15 biological and disease specificity). The purified protein may
be tested in numerous assays, typically in vitro assays, which
evaluate biologically relevant responses. See, e.g., Coligan
25 Current Protocols in Immunology; Hood, et al. Immunology
Benjamin/Cummings; Paul (ed.) Fundamental Immunology; and
20 Methods in Enzymology Academic Press.

One method of drug screening utilizes eukaryotic or
30 prokaryotic host cells which are stably transformed with
recombinant DNA molecules expressing the IL-170 antigens.
Cells may be isolated which express an antigen in isolation
25 from other functionally equivalent antigens. Such cells,
either in viable or fixed form, can be used for standard
35 protein-protein binding assays. See also, Parce, et al. (1989)
Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l
Acad. Sci. USA 87:4007-4011, which describe sensitive methods
40 to detect cellular responses. Competitive assays are
particularly useful, where the cells (source of IL-170 protein)
are contacted and incubated with a labeled binding partner or
45 antibody having known binding affinity to the ligand, such as
125I-antibody, and a test sample whose binding affinity to the
35 binding composition is being measured. The bound and free
labeled binding compositions are then separated to assess the
degree of antigen binding. The amount of test compound bound
50 is inversely proportional to the amount of labeled receptor
binding to the known source. Any one of numerous techniques

5 can be used to separate bound from free antigen to assess the
degree of binding. This separation step could typically
involve a procedure such as adhesion to filters followed by
washing, adhesion to plastic followed by washing, or
10 5 centrifugation of the cell membranes. Viable cells could also
be used to screen for the effects of drugs on IL-170 protein
mediated functions, e.g., second messenger levels, i.e., Ca^{++} ;
cell proliferation; inositol phosphate pool changes; and
15 others. Some detection methods allow for elimination of a
20 separation step, e.g., a proximity sensitive detection system.
Calcium sensitive dyes will be useful for detecting Ca^{++}
levels, with a fluorimeter or a fluorescence cell sorting
apparatus.

Another method utilizes membranes from transformed
15 eukaryotic or prokaryotic host cells as the source of the IL-
170 protein. These cells are stably transformed with DNA
vectors directing the expression of a membrane associated IL-
25 170 protein, e.g., an engineered membrane bound form.
Essentially, the membranes would be prepared from the cells and
20 used in any receptor/ligand type binding assay such as the
competitive assay set forth above.

30 Still another approach is to use solubilized, unpurified
or solubilized, purified IL-170 protein from transformed
eukaryotic or prokaryotic host cells. This allows for a
25 "molecular" binding assay with the advantages of increased
35 specificity, the ability to automate, and high drug test
throughput.

Another technique for drug screening involves an approach
40 which provides high throughput screening for compounds having
30 suitable binding affinity to IL-170 and is described in detail
in Geysen, European Patent Application 84/03564, published on
September 13, 1984. First, large numbers of different small
peptide test compounds are synthesized on a solid substrate,
45 e.g., plastic pins or some other appropriate surface, see
35 Fodor, et al. (1991). Then all the pins are reacted with
solubilized, unpurified or solubilized, purified IL-170 binding
composition, and washed. The next step involves detecting
50 bound binding composition.

5 Rational drug design may also be based upon structural studies of the molecular shapes of the IL-170 protein and other effectors or analogs. Effectors may be other proteins which mediate other functions in response to antigen binding, or
10 5 other proteins which normally interact with the antigen. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will
15 provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York.

20 Purified IL-170 protein can be coated directly onto plates for use in the aforementioned drug screening techniques.
15 However, non-neutralizing antibodies to these ligands can be used as capture antibodies to immobilize the respective ligand on the solid phase.
25

IX. Kits

20 This invention also contemplates use of IL-170 proteins, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of a binding composition. Typically the kit will have a compartment containing either a defined IL-170 peptide or
30 gene segment or a reagent which recognizes one or the other, e.g., antigen fragments or antibodies.
35

A kit for determining the binding affinity of a test compound to an IL-170 protein would typically comprise a test compound; a labeled compound, for example an antibody having
40 30 known binding affinity for the antigen; a source of IL-170 protein (naturally occurring or recombinant); and a means for separating bound from free labeled compound, such as a solid phase for immobilizing the antigen. Once compounds are
45 screened, those having suitable binding affinity to the antigen can be evaluated in suitable biological assays, as are well
35 known in the art, to determine whether they exhibit similar biological activities to the natural antigen. The availability of recombinant IL-170 protein polypeptides also provide well
50 defined standards for calibrating such assays.

5 A preferred kit for determining the concentration of, for example, an IL-170 protein in a sample would typically comprise a labeled compound, e.g., antibody, having known binding affinity for the antigen, a source of antigen (naturally
10 5 occurring or recombinant) and a means for separating the bound from free labeled compound, for example, a solid phase for immobilizing the IL-170 protein. Compartments containing reagents, and instructions, will normally be provided.

15 One method for determining the concentration of IL-170 protein in a sample would typically comprise the steps of: (1) preparing membranes from a sample comprised of a membrane bound IL-170 protein source; (2) washing the membranes and suspending
20 them in a buffer; (3) solubilizing the antigen by incubating the membranes in a culture medium to which a suitable detergent has been added; (4) adjusting the detergent concentration of the solubilized antigen; (5) contacting and incubating said
25 dilution with radiolabeled antibody to form complexes; (6) recovering the complexes such as by filtration through polyethyleneimine treated filters; and (7) measuring the
30 radioactivity of the recovered complexes.

35 Antibodies, including antigen binding fragments, specific for the IL-170 protein or fragments are useful in diagnostic applications to detect the presence of elevated levels of IL-170 protein and/or its fragments. Such diagnostic assays can
40 25 employ lysates, live cells, fixed cells, immunofluorescence, cell cultures, body fluids, and further can involve the detection of antigens related to the protein in serum, or the like. Diagnostic assays may be homogeneous (without a separation step between free reagent and protein-protein
45 30 complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT),
50 35 substrate-labeled fluorescent immunoassay (SLFIA), and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to an IL-170 protein or to a particular fragment thereof. Similar assays have also been extensively discussed

5 in the literature. See, e.g., Harlow and Lane (1988)
Antibodies: A Laboratory Manual, CSH.

Anti-idiotypic antibodies may have similar use to diagnose
presence of antibodies against an IL-170 protein, as such may
10 be diagnostic of various abnormal states. For example,
overproduction of IL-170 protein may result in production of
various immunological reactions which may be diagnostic of
abnormal physiological states, particularly in proliferative
15 cell conditions such as cancer or abnormal differentiation.

20 Frequently, the reagents for diagnostic assays are
supplied in kits, so as to optimize the sensitivity of the
assay. For the subject invention, depending upon the nature of
the assay, the protocol, and the label, either labeled or
unlabeled antibody, or labeled IL-170 protein is provided.
25 This is usually in conjunction with other additives, such as
buffers, stabilizers, materials necessary for signal production
such as substrates for enzymes, and the like. Preferably, the
kit will also contain instructions for proper use and disposal
of the contents after use. Typically the kit has compartments
20 for each useful reagent. Desirably, the reagents are provided
as a dry lyophilized powder, where the reagents may be
reconstituted in an aqueous medium providing appropriate
concentrations of reagents for performing the assay.

Any of the aforementioned constituents of the drug
25 screening and the diagnostic assays may be used without
modification or may be modified in a variety of ways. For
example, labeling may be achieved by covalently or non-
covalently joining a moiety which directly or indirectly
provides a detectable signal. In any of these assays, the
40 antigen, test compound, IL-170 protein, or antibodies thereto
can be labeled either directly or indirectly. Possibilities
for direct labeling include label groups: radiolabels such as
125I, enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and
alkaline phosphatase, and fluorescent labels (U.S. Pat. No.
45 3,940,475) capable of monitoring the change in fluorescence
intensity, wavelength shift, or fluorescence polarization.
Possibilities for indirect labeling include biotinylation of
one constituent followed by binding to avidin coupled to one of
50 the above label groups.

5 There are also numerous methods of separating the bound
from the free antigen, or alternatively the bound from the free
test compound. The IL-170 protein can be immobilized on
various matrixes followed by washing. Suitable matrixes
10 5 include plastic such as an ELISA plate, filters, and beads.
Methods of immobilizing the IL-170 protein to a matrix include,
without limitation, direct adhesion to plastic, use of a
capture antibody, chemical coupling, and biotin-avidin. The
15 last step in this approach involves the precipitation of
20 10 protein-protein complex by any of several methods including
those utilizing, e.g., an organic solvent such as polyethylene
glycol or a salt such as ammonium sulfate. Other suitable
separation techniques include, without limitation, the
20 fluorescein antibody magnetizable particle method described in
15 Rattle, et al. (1984) Clin. Chem. 30:1457-1461, and the double
antibody magnetic particle separation as described in U.S. Pat.
No. 4,659,678.

25 The methods for linking proteins or their fragments to the
various labels have been extensively reported in the literature
20 and do not require detailed discussion here. Many of the
techniques involve the use of activated carboxyl groups either
30 through the use of carbodiimide or active esters to form
peptide bonds, the formation of thioethers by reaction of a
mercapto group with an activated halogen such as chloroacetyl,
25 or an activated olefin such as maleimide, for linkage, or the
35 like. Fusion proteins will also find use in these
applications.

 Another diagnostic aspect of this invention involves use
of oligonucleotide or polynucleotide sequences taken from the
40 30 sequence of an IL-170 protein. These sequences can be used as
probes for detecting levels of antigen message in samples from
patients suspected of having an abnormal condition, e.g.,
cancer or developmental problem. The preparation of both RNA
45 and DNA nucleotide sequences, the labeling of the sequences,
35 and the preferred size of the sequences has received ample
description and discussion in the literature. Normally an
oligonucleotide probe should have at least about 14
50 nucleotides, usually at least about 18 nucleotides, and the
polynucleotide probes may be up to several kilobases. Various

5 labels may be employed, most commonly radionuclides,
particularly ^{32}P . However, other techniques may also be
employed, such as using biotin modified nucleotides for
introduction into a polynucleotide. The biotin then serves as
10 5 the site for binding to avidin or antibodies, which may be
labeled with a wide variety of labels, such as radionuclides,
fluorescers, enzymes, or the like. Alternatively, antibodies
may be employed which can recognize specific duplexes,
15 including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes,
10 or DNA-protein duplexes. The antibodies in turn may be labeled
and the assay carried out where the duplex is bound to a
surface, so that upon the formation of duplex on the surface,
20 the presence of antibody bound to the duplex can be detected.
The use of probes to the novel anti-sense RNA may be carried
15 out in any conventional techniques such as nucleic acid
hybridization, plus and minus screening, recombinational
probing, hybrid released translation (HRT), and hybrid arrested
25 translation (HART). This also includes amplification
techniques such as polymerase chain reaction (PCR). Another
20 approach utilizes, e.g., antisense nucleic acid, including the
introduction of double stranded RNA (dsRNA) to genetically
interfere with gene function as described, e.g., in Misquitta,
30 et al. (1999) Proc. Nat'l Acad. Sci. USA 96:1451-1456, and/or
ribozymes to block translation of a specific IL-70 mRNA. The
25 use of antisense methods to inhibit the in vitro translation of
genes is well known in the art. Marcus-Sakura (1988) Anal.
Biochem. 172:289; Akhtar (ed. 1995) Delivery Strategies for
Antisense Oligonucleotide Therapeutics CRC Press, Inc.

40 30 Diagnostic kits which also test for the qualitative or
quantitative presence of other markers are also contemplated.
Diagnosis or prognosis may depend on the combination of
multiple indications used as markers. Thus, kits may test for
45 combinations of markers. See, e.g., Viallet, et al. (1989)
Progress in Growth Factor Res. 1:89-97.

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50 The broad scope of this invention is best understood with
reference to the following examples, which are not intended to
limit the invention to specific embodiments.

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EXAMPLES

I. General Methods

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- Some of the standard methods are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York; Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, N.Y.; and Kohler, et al. (1995) Quantitation of mRNA by Polymerase Chain Reaction Springer-Verlag, Berlin.
- Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography, electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Deutscher (1990) "Guide to Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.) Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System QUIAGEN, Inc., Chatsworth, CA.

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- Also incorporated herein by reference is a similar patent application directed to the IL-171 and IL-175 cytokines, Attorney Docket Number DX0918P, filed on the same date as this.
- Standard immunological techniques are described, e.g., in Hertenberg, et al. (eds. 1996) Weir's Handbook of Experimental Immunology vols. 1-4, Blackwell Science; Coligan (1991) Current Protocols in Immunology Wiley/Greene, NY; and Methods in Enzymology vols. 70, 73, 74, 84, 92, 93, 108, 116, 121, 132, 150, 162, and 163. Cytokine assays are described, e.g., in

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Thomson (ed. 1998) The Cytokine Handbook (3d ed.) Academic Press, San Diego; Mire-Sluis and Thorpe (1998) Cytokines Academic Press, San Diego; Metcalf and Nicola (1995) The Hematopoietic Colony Stimulating Factors Cambridge University Press; and Aggarwal and Gutterman (1991) Human Cytokines Blackwell Pub.

Assays for vascular biological activities are well known in the art. They will cover angiogenic and angiostatic activities in tumor, or other tissues, e.g., arterial smooth muscle proliferation (see, e.g., Koyoma, et al. (1996) Cell 87:1069-1078), monocyte adhesion to vascular epithelium (see McEvoy, et al. (1997) J. Exp. Med. 185:2069-2077), etc. See also Ross (1993) Nature 362:801-809; Rekhater and Gordon (1995) Am. J. Pathol. 147:668-677; Thyberg, et al. (1990) Atherosclerosis 10:966-990; and Gumbiner (1996) Cell 84:345-357.

Assays for neural cell biological activities are described, e.g., in Wouterlood (ed. 1995) Neuroscience Protocols modules 10, Elsevier; Methods in Neurosciences Academic Press; and Neuromethods Humana Press, Totowa, NJ. Methodology of developmental systems is described, e.g., in Meisami (ed.) Handbook of Human Growth and Developmental Biology CRC Press; and Chrispeels (ed.) Molecular Techniques and Approaches in Developmental Biology Interscience.

Computer sequence analysis is performed, e.g., using available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-170 may be applied to these new entities, as described, e.g., in USSN, each of which is incorporated herein by reference for all purposes.

FACS analyses are described in Melamed, et al. (1990) Flow Cytometry and Sorting Wiley-Liss, Inc., New York, NY; Shapiro (1988) Practical Flow Cytometry Liss, New York, NY; and Robinson, et al. (1993) Handbook of Flow Cytometry Methods Wiley-Liss, New York, NY.

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II. Isolation of a DNA clone encoding IL-170 protein

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Isolation of murine CTLA-8 is described in Rouvier, et al. (1993) J. Immunol. 150:5445-5456. Similar methods are available for isolating species counterparts of the IL-173, IL-174, IL-176, and IL-177, along with the IL-171, IL-172, and IL-175.

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Source of the IL-170 messages

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Various cell lines are screened using an appropriate probe for high level message expression. Appropriate cell lines are selected based upon expression levels of the appropriate IL-170 message.

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15 Isolation of an IL-170 encoding clone

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Standard PCR techniques are used to amplify an IL-170 gene sequence from a genomic or cDNA library, or from mRNA. A human genomic or cDNA library is obtained and screened with an appropriate cDNA or synthetic probe. PCR primers may be prepared. Appropriate primers are selected, e.g., from the sequences provided, and a full length clone is isolated. Various combinations of primers, of various lengths and possibly with differences in sequence, may be prepared. The full length clone can be used as a hybridization probe to screen for other homologous genes using stringent or less stringent hybridization conditions.

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In another method, oligonucleotides are used to screen a library. In combination with polymerase chain reaction (PCR) techniques, synthetic oligonucleotides in appropriate orientations are used as primers to select correct clones from a library.

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III. Biochemical Characterization of IL-170 proteins

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An IL-170 protein is expressed in heterologous cells, e.g., the native form or a recombinant form displaying the FLAG peptide at the carboxy terminus. See, e.g., Crowe, et al. (1992) QIAexpress: The High Level Expression and Protein Purification System QIAGEN, Inc. Chatsworth, CA; and Hopp, et al. (1988) Bio/Technology 6:1204-1210. These two forms are

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introduced into expression vectors, e.g., pME18S or pEE12, and subsequently transfected into appropriate cells, e.g., COS-7 or NSO cells, respectively. Electroporated cells are cultivated, e.g., for 48 hours in RPMI medium supplemented with 10% Fetal Calf Serum. Cells are then incubated with ^{35}S -Met and ^{35}S -Cys in order to label cellular proteins. Comparison of the proteins under reducing conditions on SDS-PAGE should show that cells transfected with full length clones should secrete a polypeptide of the appropriate size, e.g., about 15,000 daltons. Treatment with endoglycosidases will demonstrate whether there are N-glycosylated forms.

IV. Large Scale Production, Purification of IL-170s

For biological assays, mammalian IL-170 is produced in large amounts, e.g., with transfected COS-7 cells grown in RPMI medium supplemented with 1% Nutridoma HU (Boehringer Mannheim, Mannheim, Germany) and subsequently purified. Purification may use affinity chromatography using antibodies, or protein purification techniques, e.g., using antibodies to determine separation properties.

In order to produce larger quantities of native proteins, stable transformants of NSO cells can be prepared according to the methodology developed by Celltech (Slough, Berkshire, UK; International Patent Applications WO86/05807, WO87/04462, WO89/01036, and WO89/10404).

Typically, 1 liter of supernatant containing human IL-173 or IL-173-FLAG is passed, e.g., on a 60 ml column of Zn^{++} ions grafted to a Chelating Sepharose Fast Flow matrix (Pharmacia, Upsalla, Sweden). After washing with 10 volumes of binding buffer (His-Bind Buffer kit, Novagen, Madison, WI), the proteins retained by the metal ions are eluted with a gradient of 20-100 mM Imidazole. The content of human IL-173-FLAG in the eluted fractions is determined by dot blot using the anti-FLAG monoclonal antibody M2 (Eastman Kodak, New Haven, CT), whereas the content of human IL-173 is assessed, e.g., by silver staining of non-reducing SDS-PAGE. The IL-170 containing fractions are then pooled and dialyzed against PBS, and are either used in biological assays or further purified, e.g., by anion exchange HPLC on a DEAE column. A third step of

5 gel filtration chromatography may be performed on a SUPERDEX G-75 HRD30 column (Pharmacia Uppsala, Sweden). Purification may be evaluated, e.g., by silver stained SDS-PAGE.

10 5 V. Preparation of antibodies against IL-173

Inbred Balb/c mice are immunized intraperitoneally, e.g., with 1 ml of purified human IL-173-FLAG emulsified in Freund's complete adjuvant on day 0, and in Freund's incomplete adjuvant on days 15 and 22. The mice are boosted with 0.5 ml of purified human IL-173 administered intravenously.

Polyclonal antiserum is collected. The serum can be purified to antibodies. The antibodies can be further processed, e.g., to Fab, Fab2, Fv, or similar fragments.

Hybridomas are created using, e.g., the non-secreting myeloma cells line SP2/0-Ag8 and polyethylene glycol 1000 (Sigma, St. Louis, MO) as the fusing agent. Hybridoma cells are placed in a 96-well Falcon tissue culture plate (Becton Dickinson, NJ) and fed with DMEM F12 (Gibco, Gaithersburg, MD) supplemented with 80 µg/ml gentamycin, 2 mM glutamine, 10% horse serum (Gibco, Gaithersburg, MD), 1% ADCM (CRTS, Lyon, France) 10^{-5} M azaserine (Sigma, St. Louis, MO) and 5×10^{-5} M hypoxanthine. Hybridoma supernatants are screened for antibody production against human IL-173 by immunocytochemistry (ICC) using acetone fixed human IL-173 transfected COS-7 cells and by ELISA using human IL-173-FLAG purified from COS-7 supernatants as a coating antigen. Aliquots of positive cell clones are expanded for 6 days and cryopreserved as well as propagated in ascites from pristane (2,6,10,14-teramethylpentadecane, Sigma, St. Louis, MO) treated Balb/c mice who had received on intraperitoneal injection of pristane 15 days before. Typically, about 10^5 hybridoma cells in 1 ml of PBS are given intraperitoneally, and 10 days later, ascites are collected from each mouse.

After centrifugation of the ascites, the antibody fraction is isolated by ammonium sulfate precipitation and anion-exchange chromatography on a Zephyr-D silicium column (IBF Sepracor) equilibrated with 20 mM Tris pH 8.0. Proteins are eluted with a NaCl gradient (ranging from 0 to 1 M NaCl). 2 ml fractions are collected and tested by ELISA for the presence of

5 anti-IL-173 antibody. The fractions containing specific anti-IL-173 activity are pooled, dialyzed, and frozen. Aliquots of the purified monoclonal antibodies may be peroxidase labeled.

10 Antibody preparations, polyclonal or monoclonal, may be cross absorbed, depleted, or combined to create reagents which exhibit desired combinations of selectivities and specificities. Defined specific antigens can be immobilized to a solid matrix and used to selectively deplete or select for
15 desired binding capacities.

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VI. Quantification of human IL-173

Among the antibodies specific for IL-173, appropriate
20 clonal isolates are selected to quantitate levels of human IL-173 using a sandwich assay. Purified antibodies are diluted,
15 e.g., at 2 $\mu\text{g/ml}$ in coating buffer (carbonate buffer, pH 9.6. 15 mM Na_2CO_3 , 35 mM NaHCO_3). This diluted solution is coated onto the wells of a 96-well ELISA plate (Immunoplate Maxisorp F96 certified, NUNC, Denmark) overnight at room temperature. The plates are then washed manually, e.g., with a washing
25 buffer consisting of Phosphate Buffered Saline and 0.05% Tween 20 (Technicon Diagnostics, USA). 110 μl of purified human CTLA-8 diluted in TBS-B-T buffer [20 mM Tris, 150 mM NaCl, 1% BSA (Sigma, St. Louis, MO), and 0.05% Tween 20] is added to each well. After 3 hours of incubation at 37° C, the plates
30 are washed once. 100 μl of peroxidase labeled Ab diluted to 5 $\mu\text{g/ml}$ in TBS-B-T buffer is added to each well, and incubated for 2 hours at 37° C. The wells are then washed three times in washing buffer. 100 μl of peroxidase substrate, 2,2' Azino-
35 bis(3 ethylbenzthiazoline-6-sulfonic acid) (ABTS), diluted to 1 mg/ml in citrate/phosphate buffer, is added to each well, and the colorimetric reaction read at 405 nm.

VII. Distribution of IL-170 genes

45 The human IL-173 was identified from sequence derived from a cDNA library from an epileptic brain frontal cortex. The rat
35 IL-173 was derived from a cDNA library from cochlea, brain, cerebellum, eye, lung, and kidney. Again, the genes appear to be quite rare, which suggests the expression distributions
50 would be highly restricted.

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5 The mouse IL-174 was identified from sequence derived from a cDNA library derived from a mouse embryo. The gene appears to be quite rare, which suggests the expression distribution would be highly restricted.

10 5 The human IL-171 was identified from a sequence derived from an apoptotic T cell. The gene appears to be quite rare, which suggests the expression distribution would be highly restricted.

15 10 The human IL-172 was identified from sequences derived from human fetal heart, liver and spleen, thymus, thymus tumor, and total fetus. Mouse was derived from sequences derived from mouse, embryo, mammary gland, and pooled organs. Both genes appear to be quite rare, which suggests their expression distribution would be highly restricted.

20 15 The human IL-175 was identified from a sequence derived from a 12 h thiouridine activated T cell. The gene appears to be quite rare, which suggests the expression distribution would be highly restricted.

20 VIII. Chromosome mapping of IL-170 genes

30 An isolated cDNA encoding the appropriate IL-170 gene is used. Chromosome mapping is a standard technique. See, e.g., BIOS Laboratories (New Haven, CT) and methods for using a mouse somatic cell hybrid panel with PCR.

35 25 The human IL-173 gene maps to human chromosome 13q11.

IX. Isolating IL-170 Homologues

40 30 A binding composition, e.g., antibody, is used for screening of an expression library made from a cell line which expresses an IL-170 protein. Standard staining techniques are used to detect or sort intracellular or surface expressed antigen, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or
45 35 immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

50 Similar methods are applicable to isolate either species or allelic variants. Species variants are isolated using cross-species hybridization techniques based upon a full

5 length isolate or fragment from one species as a probe, or appropriate species.

X. Isolating receptors for IL-170

10 5 Methods are available for screening of an expression library made from a cell line which expresses potential IL-170 receptors. A labeled IL-170 ligand is produced, as described above. Standard staining techniques are used to
15 detect or sort surface expressed receptor, or surface
10 expressing transformed cells are screened by panning. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.

For example, on day 0, precoat 2-chamber permanox slides
20 with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate
15 COS cells at $2-3 \times 10^5$ cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.

On day 1 for each sample, prepare 0.5 ml of a solution
25 of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is
20 prepared, e.g., of huIL-170-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with serum free
30 DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and
25 incubate overnight.

On day 2, change the medium. On days 3 or 4, the cells
35 are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS.
40 30 The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M NaN₃ for 20 min. Cells are then washed with HBSS/saponin 1X.
45 Soluble antibody is added to cells and incubate for 30 min.
35 Wash cells twice with HBSS/saponin. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector
50 Elite ABC horseradish peroxidase solution, and preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1

5 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells
twice with HBSS/saponin. Add ABC HRP solution and incubate
for 30 min. Wash cells twice with HBSS, second wash for 2
10 min, which closes cells. Then add Vector diaminobenzoic acid
5 (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops
DAB plus 2 drops of H₂O₂ per 5 ml of glass distilled water.
Carefully remove chamber and rinse slide in water. Air dry
for a few minutes, then add 1 drop of Crystal Mount and a
15 cover slip. Bake for 5 min at 85-90° C.

20 Alternatively, the labeled ligand is used to affinity
purify or sort out cells expressing the receptor. See, e.g.,
Sambrook, et al. or Ausubel, et al.

20 All references cited herein are incorporated herein by
15 reference to the same extent as if each individual
publication or patent application was specifically and
individually indicated to be incorporated by reference.

25 Many modifications and variations of this invention can
be made without departing from its spirit and scope, as will
20 be apparent to those skilled in the art. The specific
embodiments described herein are offered by way of example
30 only, and the invention is to be limited only by the terms of
the appended claims, along with the full scope of equivalents
to which such claims are entitled.

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Claims

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WHAT IS CLAIMED IS:

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1. An isolated or recombinant polynucleotide comprising sequence selected from the group consisting of:

5 a) a mammalian IL-173 sequence which:

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- i) encodes at least 8 contiguous amino acids of mature SEQ ID NO: 6, 8, 10, or 12;
- ii) encodes at least two distinct segments of at least 5 contiguous amino acids of mature SEQ ID NO: 6, 8, 10, or 12; or
- iii) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 5, 7, 9, or 11;

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b) a mammalian IL-174 sequence which:

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- i) encodes at least 8 contiguous amino acids of mature SEQ ID NO: 14, 16, or 18;
- ii) encodes at least two distinct segments of at least 5 contiguous amino acids of mature SEQ ID NO: 14, 16, or 18; or
- iii) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 14, 16, or 18;

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c) a mammalian IL-176 sequence which:

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- i) encodes at least 8 contiguous amino acids of mature SEQ ID NO: 28;
- ii) encodes at least two distinct segments of at least 5 contiguous amino acids of mature SEQ ID NO: 28; or
- iii) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 27; and

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d) a mammalian IL-177 sequence which:

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- i) encodes at least 8 contiguous amino acids of mature SEQ ID NO: 30;
- ii) encodes at least two distinct segments of at least 5 contiguous amino acids of mature SEQ ID NO: 30; or
- iii) comprises one or more segments at least 21 contiguous nucleotides of SEQ ID NO: 29.

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2. The polynucleotide of Claim 1 in an expression vector, comprising a sequence selected from the group consisting of:

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- 5 a) an IL-173 sequence which:
- 10 i) encodes at least 12 contiguous amino acids of SEQ ID NO: 6, 8, 10, or 12;
 - 15 ii) encodes at least two distinct segments of at least 7 and 10 contiguous amino acids of SEQ ID NO: 6, 8, 10, or 12; or
 - 20 iii) comprises at least 27 contiguous nucleotides of SEQ ID NO: 5, 7, 9, or 11;
- 25 b) an IL-174 sequence which:
- 30 i) encodes at least 12 contiguous amino acids of SEQ ID NO: 14, 16, or 18;
 - 35 ii) encodes at least two distinct segments of at least 7 and 10 contiguous amino acids of SEQ ID NO: 14, 16, or 18; or
 - 40 iii) comprises at least 27 contiguous nucleotides of SEQ ID NO: 13, 15, or 17;
- 45 c) an IL-176 sequence which:
- 50 i) encodes at least 12 contiguous amino acids of SEQ ID NO: 28;
 - 55 ii) encodes at least two distinct segments of at least 7 and 10 contiguous amino acids of SEQ ID NO: 28; or
 - 60 iii) comprises at least 27 contiguous nucleotides of SEQ ID NO: 27; and
- 65 d) an IL-177 sequence which:
- 70 i) encodes at least 12 contiguous amino acids of SEQ ID NO: 30;
 - 75 ii) encodes at least two distinct segments of at least 7 and 10 contiguous amino acids of SEQ ID NO: 30; or
 - 80 iii) comprises at least 27 contiguous nucleotides of SEQ ID NO: 29.
- 85 3. The polynucleotide of Claim 2 selected from the group consisting of:
- 90 a) an IL-173 sequence which:
- 95 i) encodes at least 16 contiguous amino acid residues of mature SEQ ID NO: 6, 8, 10, or 12;
 - 100 ii) encodes at least two distinct segments of at least 10 and 13 contiguous amino acid residues of mature SEQ ID NO: 6, 8, 10, or 12;

- 5 iii) comprises at least 33 contiguous nucleotides of SEQ
ID NO: 5, 7, 9, or 11; or
- 10 iv) comprises the entire mature coding portion of SEQ ID
NO: 5, 7, 9, or 11;
- 10 5 b) an IL-174 sequence which:
- i) encodes at least 16 contiguous amino acid residues of
mature SEQ ID NO: 14, 16, or 18;
- 15 ii) encodes at least two distinct segments of at least 10
and 13 contiguous amino acid residues of mature SEQ
10 ID NO: 14, 16, or 18; or
- iii) comprises at least 33 contiguous nucleotides of SEQ
ID NO: 13, 15, or 17; or
- 20 iv) comprises the entire mature coding portion of SEQ ID
NO: 13, 15, or 17;
- 15 c) an IL-176 sequence which:
- i) encodes at least 16 contiguous amino acids of mature
25 SEQ ID NO: 28;
- ii) encodes at least two distinct segments of at least 10
and 14 contiguous amino acid residues of mature SEQ
20 ID NO: 28;
- iii) comprises at least 33 contiguous nucleotides of SEQ
30 ID NO: 27; or
- iv) comprises the entire mature coding portion of SEQ ID
NO: 27; and
- 25 d) an IL-177 sequence which:
- i) encodes at least 16 contiguous amino acids of mature
35 SEQ ID NO: 30;
- ii) encodes at least two distinct segments of at least 10
and 14 contiguous amino acid residues of mature SEQ
40 ID NO: 30;
- iii) comprises at least 33 contiguous nucleotides of SEQ
30 ID NO: 29; or
- iv) comprises the entire mature coding portion of SEQ ID
45 NO: 29.

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- 5 4. A method of making:
- a) a polypeptide comprising expressing said expression
 vector of Claim 2, thereby producing said
 polypeptide;
- 10 5 b) a duplex nucleic acid comprising contacting a
 polynucleotide of Claim 2 with a complementary
 nucleic acid, thereby resulting in production of said
 duplex nucleic acid; or
- 15 c) a polynucleotide of Claim 2 comprising amplifying
20 using a PCR method.
5. An isolated or recombinant polynucleotide which
20 hybridizes under stringent wash conditions of at least 55° C
 and less than 400 mM salt to:
- 15 a) the (IL-173) polynucleotide of Claim 3 which consists
 of the mature coding portions of SEQ ID NO: 5, 7, 9,
25 or 11;
- b) the (IL-174) polynucleotide of Claim 3 which consists
 of the mature coding portions of SEQ ID NO: 13, 15,
20 or 17; or
- c) the (IL-176) polynucleotide of Claim 3 which consists
30 of the mature coding portions of SEQ ID NO: 27; or
- d) the (IL-177) polynucleotide of Claim 3 which consists
 of the mature coding portions of SEQ ID NO: 29.
- 25 25 6. A polynucleotide of Claim 5:
- a) wherein said wash conditions are at least 65° C and
 less than 300 mM salt; or
- 40 30 b) which comprises at least 50 contiguous nucleotides of
 the mature coding portion of:
- i) SEQ ID NO: 5, 7, 9, or 11 (IL-173);
- ii) SEQ ID NO: 13, 15, or 17 (IL-174);
- 45 iii) SEQ ID NO: 27 (IL-176); or
- iv) SEQ ID NO: 29 (IL-177).
- 35 35 7. A kit comprising said polynucleotide of Claim 6, and
- a) instructions for the use of said polynucleotide for
50 detection;
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- 5 b) instructions for the disposal of said polynucleotide
 or other reagents of said kit; or
 c) both a and b.

10 5 8. A cell containing said expression vector of Claim 3,
 wherein said cell is:

- a) a prokaryotic cell;
 b) a eukaryotic cell;
15 c) a bacterial cell;
 d) a yeast cell;
 e) an insect cell;
 f) a mammalian cell;
20 g) a mouse cell;
 h) a primate cell; or
15 i) a human cell.

25 9. An isolated or recombinant antigenic polypeptide:

- a) (IL-173) comprising at least:
 i) one segment of 8 identical contiguous amino acids from
20 the mature coding portions of SEQ ID NO: 6, 8, 10, or
 12; or
30 ii) two distinct segments of at least 5 contiguous amino
 acids from the mature coding portions of SEQ ID NO:
 6, 8, 10, or 12; or
25 b) (IL-174) comprising at least:
35 i) one segment of 8 identical contiguous amino acids from
 the mature coding portions of SEQ ID NO: 14, 16, or
 18; or
40 ii) two distinct segments of at least 5 contiguous amino
30 acids from the mature coding portions of SEQ ID NO:
 14, 16, or 18.
 c) (IL-176) comprising at least:
45 i) one segment of 8 identical contiguous amino acids from
 the mature coding portions of SEQ ID NO: 28; or
35 ii) two distinct segments of at least 5 contiguous amino
 acids from the mature coding portions of SEQ ID NO:
 28;

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- 5 d) (IL-177) comprising at least:
- 10 i) one segment of 8 identical contiguous amino acids from
the mature coding portions of SEQ ID NO: 30; or
 - 15 ii) two distinct segments of at least 5 contiguous amino
acids from the mature coding portions of SEQ ID NO:
30.
- 20 10. The polypeptide of Claim 9, wherein:
- 15 a) said segment of 8 identical contiguous amino acids is
at least 14 contiguous amino acids; or
 - 20 b) one of said segments of at least 5 contiguous amino
acids comprises at least 7 contiguous amino acids.
- 25 11. The polypeptide of Claim 9, wherein:
- 30 15 A) (IL-173) said polypeptide:
- a) comprises SEQ ID NO: 6, 8, 10, or 12;
 - 25 b) binds with selectivity to a polyclonal antibody
generated against an immunogen of the mature SEQ ID
NO: 6, 8, 10, or 12;
 - 20 c) comprises a plurality of distinct polypeptide segments
of 10 contiguous amino acids of the mature SEQ ID NO:
30 6, 8, 10, or 12;
 - d) is a natural allelic variant of SEQ ID NO: 8 or 12;
 - e) has a length at least 30 amino acids; or
 - 25 f) exhibits at least two non-overlapping epitopes which
are selective for the mature SEQ ID NO: 6, 8, 10, or
35 12;
- 40 B) (IL-174) said polypeptide:
- a) comprises the mature SEQ ID NO: 14, 16, or 18;
 - 30 b) binds with selectivity to a polyclonal antibody
generated against an immunogen of the mature SEQ ID
NO: 14, 16, or 18;
 - 45 c) comprises a plurality of distinct polypeptide segments
of 10 contiguous amino acids of the mature SEQ ID NO:
35 14, 16, or 18;
 - d) is a natural allelic variant of SEQ ID NO: 14 or 18;
 - 50 e) has a length at least 30 amino acids; or
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- 5 f) exhibits at least two non-overlapping epitopes which
are selective for primate protein of the mature SEQ
ID NO: 14, 16, or 18;
- 10 C) (IL-176) said polypeptide:
- 5 a) comprises a mature sequence of SEQ ID NO: 28;
- b) binds with selectivity to a polyclonal antibody
generated against an immunogen of the mature SEQ ID
NO: 28;
- 15 c) comprises a plurality of distinct polypeptide segments
10 of 10 contiguous amino acids of the mature SEQ ID NO:
28;
- d) is a natural allelic variant of SEQ ID NO: 28;
- 20 e) has a length at least 30 amino acids; or
- f) exhibits at least two non-overlapping epitopes which
15 are selective for the mature SEQ ID NO: 28; or
- D) (IL-177) said polypeptide:
- 25 a) comprises a mature sequence of SEQ ID NO: 30;
- b) binds with selectivity to a polyclonal antibody
generated against an immunogen of the mature SEQ ID
20 NO: 30;
- c) comprises a plurality of distinct polypeptide segments
30 of 10 contiguous amino acids of the mature SEQ ID NO:
30;
- d) is a natural allelic variant of SEQ ID NO: 30;
- 35 e) has a length at least 30 amino acids; or
- f) exhibits at least two non-overlapping epitopes which
are selective for the mature SEQ ID NO: 30.
- 40 12. The polypeptide of Claim 11, which:
- 30 a) is in a sterile composition;
- b) is not glycosylated;
- c) is denatured;
- 45 d) is a synthetic polypeptide;
- e) is attached to a solid substrate;
- 35 f) is a fusion protein with a detection or purification
tag;
- g) is a 5-fold or less substitution from a natural
50 sequence; or
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- 5 h) is a deletion or insertion variant from a natural sequence.
- 10 13. A method using said polypeptide of Claim 9:
- 5 a) to label said polypeptide, comprising labeling said polypeptide with a radioactive label;
- 15 b) to separate said polypeptide from another polypeptide in a mixture, comprising running said mixture on a chromatography matrix, thereby separating said polypeptides;
- 10 c) to identify a compound that binds selectively to said polypeptide, comprising incubating said compound with said polypeptide under appropriate conditions; thereby causing said compound to bind to said polypeptide; or
- 20 d) to conjugate said polypeptide to a matrix, comprising derivatizing said polypeptide with a reactive reagent, and conjugating said polypeptide to said matrix.
- 15 20
- 30 14. A binding compound comprising an antigen binding portion from an antibody which binds with selectivity to said polypeptide of Claim 11, wherein said polypeptide:
- 35 25 a) (IL-173) comprises the mature SEQ ID NO 6, 8, 10, or 12; or
- b) (IL-174) comprises the mature SEQ ID NO 14, 16, or 18;
- c) (IL-176) comprises the mature SEQ ID NO 28; or
- d) (IL-177) comprises the mature SEQ ID NO 30.
- 40 30 15. The binding compound of Claim 14, wherein said antibody is a polyclonal antibody which is raised against:
- 45 a) (IL-173) SEQ ID NO: 6, 8, 10, or 12; or
- b) (IL-174) SEQ ID NO: 14, 16, or 18;
- 35 c) (IL-176) SEQ ID NO: 28; or
- d) (IL-177) SEQ ID NO: 30.
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- 5 16. The binding compound of Claim 14, wherein said:
- 10 a) antibody:
- 5 i) is immunoselected;
- 10 ii) binds to a denatured protein; or
- 10 iii) exhibits a K_d to said polypeptide of at least 30 mM; or
- 15 b) said binding compound:
- 15 i) is attached to a solid substrate, including a bead or plastic membrane;
- 10 ii) is in a sterile composition; or
- 20 iii) is detectably labeled, including a radioactive or fluorescent label.
- 15 17. A method of producing an antigen:antibody complex, comprising contacting a polypeptide comprising sequence from SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 28, or 30 with a binding compound of Claim 14 under conditions which allow said complex to form.
- 20 18. The method of Claim 17, wherein said binding compound is an antibody, and said polypeptide is in a biological sample.
- 30 19. A kit comprising said binding compound of Claim 14 and:
- 35 a) a polypeptide of the mature SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 28, or 30;
- 40 b) instructions for the use of said binding compound for detection; or
- 30 c) instructions for the disposal of said binding compound or other reagents of said kit.
- 45 20. A method of evaluating the selectivity of binding of an antibody to a protein of the mature SEQ ID NO: 6, 8, 10, 12, 14, 16, 18, 28, or 30, comprising contacting said antibody to said protein and to another cytokine; and comparing binding of said antibody to said protein and said cytokine.
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SEQUENCE LISTING

SEQ ID NO: 1 is primate IL-172 nucleic acid sequence.
SEQ ID NO: 2 is primate IL-172 polypeptide sequence.
SEQ ID NO: 3 is murine IL-172 nucleic acid sequence.
SEQ ID NO: 4 is murine IL-172 polypeptide sequence.
SEQ ID NO: 5 is primate IL-173 nucleic acid sequence.
SEQ ID NO: 6 is primate IL-173 polypeptide sequence.
SEQ ID NO: 7 is supplementary primate IL-173 nucleic acid sequence.
SEQ ID NO: 8 is supplementary primate IL-173 polypeptide sequence.
SEQ ID NO: 9 is murine IL-173 nucleic acid sequence.
SEQ ID NO: 10 is murine IL-173 polypeptide sequence.
SEQ ID NO: 11 is supplementary murine IL-173 nucleic acid sequence.
SEQ ID NO: 12 is supplementary murine IL-173 polypeptide sequence.
SEQ ID NO: 13 is primate IL-174 nucleic acid sequence.
SEQ ID NO: 14 is primate IL-174 polypeptide sequence.
SEQ ID NO: 15 is murine IL-174 nucleic acid sequence.
SEQ ID NO: 16 is murine IL-174 polypeptide sequence.
SEQ ID NO: 17 is supplementary murine IL-174 nucleic acid sequence.
SEQ ID NO: 18 is supplementary murine IL-174 polypeptide sequence.
SEQ ID NO: 19 is primate IL-171 IUPAC nucleic acid sequence.
SEQ ID NO: 20 is primate IL-171 nucleic acid sequence.
SEQ ID NO: 21 is primate IL-171 polypeptide sequence.
SEQ ID NO: 22 is supplementary primate IL-171 nucleic acid sequence.
SEQ ID NO: 23 is supplementary primate IL-171 polypeptide sequence.
SEQ ID NO: 24 is primate IL-175 IUPAC nucleic acid sequence.
SEQ ID NO: 25 is primate IL-175 nucleic acid sequence.
SEQ ID NO: 26 is primate IL-175 polypeptide sequence.
SEQ ID NO: 27 is primate IL-176 nucleic acid sequence.
SEQ ID NO: 28 is primate IL-176 polypeptide sequence.
SEQ ID NO: 29 is primate IL-177 nucleic acid sequence.
SEQ ID NO: 30 is primate IL-177 polypeptide sequence.
SEQ ID NO: 31 is rat CTLA-8 polypeptide sequence.
SEQ ID NO: 32 is mouse CTLA-8 polypeptide sequence.
SEQ ID NO: 33 is primate CTLA-8 polypeptide sequence.
SEQ ID NO: 34 is viral CTLA-8 polypeptide sequence.

<110> Schering Corporation

<120> Purified Mammalian Cytokines; Related Reagents and
Methods

<130> DX0917K

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<150> USSN 09/228,822

<151> 1999-01-11

<160> 34

<170> PatentIn Ver. 2.1

<210> 1

<211> 543

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<213> primate

<220>

<221> CDS

<222> (1)..(540)

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<221> mat_peptide

<222> (61)..(540)

<400> 1

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-20 -15 -10 -5

ctg ggg ctg ggc cag ccc agg agc ccc aaa agc aag agg aag ggg caa 96
Leu Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln
-1 1 5 10

ggg cgg cct ggg ccc ctg gtc cct ggc cct cac cag gtg cca ctg gac 144
Gly Arg Pro Gly Pro Leu Val Pro Gly Pro His Gln Val Pro Leu Asp
15 20 25

ctg gtg tca cgg atg aaa ccg tat gcc cgc atg gag gag tat gag agg 192
Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
30 35 40

aac atc gag gag atg gtg gcc cag ctg agg aac agc tca gag ctg gcc 240
Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala
45 50 55 60

cag aga aag tgt gag gtc aac ttg cag ctg tgg atg tcc aac aag agg 288
Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg
65 70 75

agc ctg tct ccc tgg ggc tac agc atc aac cac gac ccc agc cgt atc 336
Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
80 85 90

ccc gtg gac ctg ccg gag gca cgg tgc ctg tgt ctg ggc tgt gtg aac 384
Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
95 100 105

ccc ttc acc atg cag gag gac cgc agc atg gtg agc gtg ccg gtg ttc 432
Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
110 115 120

agc cag gtt cct gtg cgc cgc cgc ctc tgc ccg cca ccg ccc cgc aca 480
Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr
125 130 135 140

ggg cct tgc cgc cag cgc gca gtc atg gag acc atc gct gtg ggc tgc 528
Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys
145 150 155

acc tgc atc ttc tga 543
Thr Cys Ile Phe
160

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<210> 2

<211> 180

<212> PRT

<213> primate

<400> 2

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Met Asp Trp Pro His Asn Leu Leu Phe Leu Leu Thr Ile Ser Ile Phe
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Leu Gly Leu Gly Gln Pro Arg Ser Pro Lys Ser Lys Arg Lys Gly Gln
      -1  1          5          10

Gly Arg Pro Gly Pro Leu Val Pro Gly Pro His Gln Val Pro Leu Asp
      15          20          25

Leu Val Ser Arg Met Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
      30          35          40

Asn Ile Glu Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Leu Ala
      45          50          55          60

Gln Arg Lys Cys Glu Val Asn Leu Gln Leu Trp Met Ser Asn Lys Arg
      65          70          75

Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
      80          85          90

Pro Val Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
      95          100          105

Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
      110          115          120

Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Pro Pro Pro Arg Thr
      125          130          135          140

Gly Pro Cys Arg Gln Arg Ala Val Met Glu Thr Ile Ala Val Gly Cys
      145          150          155

Thr Cys Ile Phe
      160

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<210> 3

<211> 543

<212> DNA

<213> rodent

<220>

<221> CDS

<222> (1)..(540)

<220>

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<222> (67)..(540)

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Met Asp Trp Pro His Ser Leu Leu Phe Leu Leu Ala Ile Ser Ile Phe
      -20          -15          -10

ctg gcg cca agc cac ccc cgg aac acc aaa ggc aaa aga aaa ggg caa      96
Leu Ala Pro Ser His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln
      -5          -1  1          5          10

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ggg agg ccc agt ccc ttg gcc cct ggg cct cat cag gtg ccg ctg gac 144
Gly Arg Pro Ser Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp
               15                20                25

ctg gtg tct cga gta aag ccc tac gct cga atg gaa gag tat gag cgg 192
Leu Val Ser Arg Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
               30                35                40

aac ctt ggg gag atg gtg gcc cag ctg agg aac agc tcc gag cca gcc 240
Asn Leu Gly Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala
               45                50                55

aag aag aaa tgt gaa gtc aat cta cag ctg tgg ttg tcc aac aag agg 288
Lys Lys Lys Cys Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg
               60                65                70

agc ctg tcc cca tgg ggc tac agc atc aac cac gac ccc agc cgc atc 336
Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
               75                80                85                90

cct gcg gac ttg ccc gag gcg cgg tgc cta tgt ttg ggt tgc gtg aat 384
Pro Ala Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
               95                100                105

ccc ttc acc atg cag gag gac cgt agc atg gtg agc gtg cca gtg ttc 432
Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
               110                115                120

agc cag gtg ccg gtg cgc cgc cgc ctc tgt cct caa cct cct cgc cct 480
Ser Gln Val Pro Val Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro
               125                130                135

ggg ccc tgc cgc cag cgt gtc gtc atg gag acc atc gct gtg ggt tgc 528
Gly Pro Cys Arg Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys
               140                145                150

acc tgc atc ttc tga 543
Thr Cys Ile Phe
155

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<210> 4
 <211> 180
 <212> PRT
 <213> rodent

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<400> 4
Met Asp Trp Pro His Ser Leu Leu Phe Leu Leu Ala Ile Ser Ile Phe
      -20                -15                -10

Leu Ala Pro Ser His Pro Arg Asn Thr Lys Gly Lys Arg Lys Gly Gln
      -5                -1  1                5                10

Gly Arg Pro Ser Pro Leu Ala Pro Gly Pro His Gln Val Pro Leu Asp
               15                20                25

Leu Val Ser Arg Val Lys Pro Tyr Ala Arg Met Glu Glu Tyr Glu Arg
               30                35                40

Asn Leu Gly Glu Met Val Ala Gln Leu Arg Asn Ser Ser Glu Pro Ala

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45 50 55
 Lys Lys Lys Cys Glu Val Asn Leu Gln Leu Trp Leu Ser Asn Lys Arg
 60 65 70
 Ser Leu Ser Pro Trp Gly Tyr Ser Ile Asn His Asp Pro Ser Arg Ile
 75 80 85 90
 Pro Ala Asp Leu Pro Glu Ala Arg Cys Leu Cys Leu Gly Cys Val Asn
 95 100 105
 Pro Phe Thr Met Gln Glu Asp Arg Ser Met Val Ser Val Pro Val Phe
 110 115 120
 Ser Gln Val Pro Val Arg Arg Arg Leu Cys Pro Gln Pro Pro Arg Pro
 125 130 135
 Gly Pro Cys Arg Gln Arg Val Val Met Glu Thr Ile Ala Val Gly Cys
 140 145 150
 Thr Cys Ile Phe
 155

<210> 5
 <211> 454
 <212> DNA
 <213> primate

<220>
 <221> CDS
 <222> (1)..(453)

<400> 5
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 Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu
 1 5 10 15
 gcg gcc ggc gtg ctc agt gcc ttc cac cac acg ctg cag ctg ggg ccg 96
 Ala Ala Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro
 20 25 30
 cgt gag cag gcg cgc aac gcg agc tgc ccg gca ggg ggc agg ccc gcc 144
 Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala
 35 40 45
 gac cgc cgc ttc cgg acg ccc acc aac ctg cgc agc gtg tcg ccc tgg 192
 Asp Arg Arg Phe Arg Thr Pro Thr Asn Leu Arg Ser Val Ser Pro Trp
 50 55 60
 gcc tac aga atc tcc tac gac ccg gcg agg tac ccc agg tac ctg cct 240
 Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro
 65 70 75 80
 gaa gcc tac tgc ctg tgc cgg ggc tgc ctg acc ggg ctg ttc ggc gag 288
 Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu
 85 90 95
 gag gac gtg cgc ttc cgc agc gcc cct gtc tac atg ccc acc gtc gtc 336
 Glu Asp Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val
 100 105 110

ctg cgc cgc acc ccc gcc tgc gcc gcc gcc cgt tcc gtc tac acc gag 384
Leu Arg Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu
115 120 125

gcc tac gtc acc atc ccc gtg gcc tgc acc tgc gtc ccc gag ccg gag 432
Ala Tyr Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu
130 135 140

aag gac gca gac agc atc aac t 454
Lys Asp Ala Asp Ser Ile Asn
145 150

<210> 6
<211> 151
<212> PRT
<213> primate

<400> 6
Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu
1 5 10 15
Ala Ala Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro
20 25 30
Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala
35 40 45
Asp Arg Arg Phe Arg Thr Pro Thr Asn Leu Arg Ser Val Ser Pro Trp
50 55 60
Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro
65 70 75 80
Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu
85 90 95
Glu Asp Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val
100 105 110
Leu Arg Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu
115 120 125
Ala Tyr Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu
130 135 140
Lys Asp Ala Asp Ser Ile Asn
145 150

<210> 7
<211> 1385
<212> DNA
<213> primate

<220>
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<220>

<221> mat_peptide
<222> (110)..(664)

<400> 7

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atg ctg gta gcc ggc ttc ctg ctg gcg ctg ccg ccg agc tgg gcc gcg 106
Met Leu Val Ala Gly Phe Leu Leu Ala Leu Pro Pro Ser Trp Ala Ala
-15 -10 -5

ggc gcc ccg agg gcg ggc agg cgc ccc gcg cgg ccg cgg ggc tgc gcg 154
Gly Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala
-1 1 5 10 15

gac cgg ccg gag gag cta ctg gag cag ctg tac ggg cgc ctg gcg gcc 202
Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala
20 25 30

ggc gtg ctc agt gcc ttc cac cac acg ctg cag ctg ggg ccg cgt gag 250
Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu
35 40 45

cag gcg cgc aac gcg agc tgc ccg gca ggg ggc agg ccc gcc gac cgc 298
Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg
50 55 60

cgc ttc cgg ccg ccc acc aac ctg cgc agc gtg tgc ccc tgg gcc tac 346
Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr
65 70 75

aga atc tcc tac gac ccg gcg agg tac ccc agg tac ctg cct gaa gcc 394
Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala
80 85 90 95

tac tgc ctg tgc cgg ggc tgc ctg acc ggg ctg ttc ggc gag gag gac 442
Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp
100 105 110

gtg cgc ttc cgc agc gcc cct gtc tac atg ccc acc gtc gtc ctg cgc 490
Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg
115 120 125

cgc acc ccc gcc tgc gcc ggc ggc cgt tcc gtc tac acc gag gcc tac 538
Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
130 135 140

gtc acc atc ccc gtg ggc tgc acc tgc gtc ccc gag ccg gag aag gac 586
Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
145 150 155

gca gac agc atc aac tcc agc atc gac aaa cag ggc gcc aag ctc ctg 634
Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu
160 165 170 175

ctg ggc ccc aac gac gcg ccc gct ggc ccc tgaggccgggt cctgccccgg 684
Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
180 185

gaggctctccc cgcccccat cccgaggcgc ccaagctgga gccgcctgga gggctcggtc 744

ggcgacctct gaagagagtg caccgagcaa accaagtgcc ggagcaccag cgccgccttt 804

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ccatggagac tcgtaagcag cttcatctga cacgggcac cctggcctgc ttttagctac 864
aagcaagcag cgtggctgga agctgatggg aaacgaccgc gcacgggcat cctgtgtgcg 924
gcccgcacatg aggggtttgga aaagtccacg gaggtccctc gaggagcctc tcagatcggc 984
tgctgcgggt gcagggcgtg actcaccgct ggggtcctgc caaagagata gggacgcata 1044
tgctttttta agcaatctaa aaataataat aagtatagcg actatatacc tacttttaaa 1104
atcaactggt ttgaatagag gcagagctat tttatattat caaatgagag ctactctggt 1164
acatttctta acatataaac atcggttttt acttcttctg gtagaatttt ttaaagcata 1224
attggaatcc ttggataaat ttgtagctg gtacactctg gcctgggtct ctgaattcag 1284
cctgtcaccg atggctgact gatgaaatgg acacgtctca tctgaccac tcttccttc 1344
actgaaggtc ttcacgggcc tccaggcctc gtgccgaatt c 1385

<210> 8
<211> 202
<212> PRT
<213> primate

<400> 8
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Gly Ala Pro Arg Ala Gly Arg Arg Pro Ala Arg Pro Arg Gly Cys Ala
-1 1 5 10 15
Asp Arg Pro Glu Glu Leu Leu Glu Gln Leu Tyr Gly Arg Leu Ala Ala
20 25 30
Gly Val Leu Ser Ala Phe His His Thr Leu Gln Leu Gly Pro Arg Glu
35 40 45
Gln Ala Arg Asn Ala Ser Cys Pro Ala Gly Gly Arg Pro Ala Asp Arg
50 55 60
Arg Phe Arg Pro Pro Thr Asn Leu Arg Ser Val Ser Pro Trp Ala Tyr
65 70 75
Arg Ile Ser Tyr Asp Pro Ala Arg Tyr Pro Arg Tyr Leu Pro Glu Ala
80 85 90 95
Tyr Cys Leu Cys Arg Gly Cys Leu Thr Gly Leu Phe Gly Glu Glu Asp
100 105 110
Val Arg Phe Arg Ser Ala Pro Val Tyr Met Pro Thr Val Val Leu Arg
115 120 125
Arg Thr Pro Ala Cys Ala Gly Gly Arg Ser Val Tyr Thr Glu Ala Tyr
130 135 140
Val Thr Ile Pro Val Gly Cys Thr Cys Val Pro Glu Pro Glu Lys Asp
145 150 155
Ala Asp Ser Ile Asn Ser Ser Ile Asp Lys Gln Gly Ala Lys Leu Leu

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160              165              170              175
Leu Gly Pro Asn Asp Ala Pro Ala Gly Pro
              180              185

<210> 9
<211> 133
<212> DNA
<213> rodent

<220>
<221> CDS
<222> (1)..(132)

<400> 9
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Phe Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu
  1              5              10              15

acc ggg ctc tac ggt gag gag gac ttc cgc ttt cgc agc gca ccc gtc 96
Thr Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Ala Pro Val
              20              25              30

ttc tct ccg gcg gtg gtg ctg cgg cgc acg gcg gcc t 133
Phe Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala
  35              40

<210> 10
<211> 44
<212> PRT
<213> rodent

<400> 10
Phe Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu
  1              5              10              15

Thr Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Ala Pro Val
              20              25              30

Phe Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala
  35              40

<210> 11
<211> 1143
<212> DNA
<213> rodent

<220>
<221> CDS
<222> (1)..(615)

<220>
<221> mat_peptide
<222> (73)..(615)

<400> 11
atg ttg ggg aca ctg gtc tgg atg ctc ctc gtc ggc ttc ctg ctg gca 48
Met Leu Gly Thr Leu Val Trp Met Leu Leu Val Gly Phe Leu Leu Ala

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	-20		-15		-10	
ctg gcg ccg ggc cgc gcg gcg ggc gcg				ctg agg acc ggg agg cgc ccg	96	
Leu Ala Pro Gly Arg Ala Ala Gly Ala			Leu Arg Thr Gly Arg Arg Pro			
	-5		-1 1		5	
gcg ccg ccg ccg gac tgc gcg gac ccg			cca gag gag ctc ctg gag cag	144		
Ala Arg Pro Arg Asp Cys Ala Asp Arg			Pro Glu Glu Leu Leu Glu Gln			
	10		15	20		
ctg tac ggg ccg ctg gcg gcc ggc gtg			ctc agc gcc ttc cac cac acg	192		
Leu Tyr Gly Arg Leu Ala Ala Gly Val			Leu Ser Ala Phe His His Thr			
	25		30	35		40
ctg cag ctc ggg ccg cgc gag cag gcg			cgc aat gcc agc tgc ccg gcc	240		
Leu Gln Leu Gly Pro Arg Glu Gln Ala			Arg Asn Ala Ser Cys Pro Ala			
		45	50	55		
ggg ggc agg gcc gcc gac cgc cgc ttc			ccg cca ccc acc aac ctg cgc	288		
Gly Gly Arg Ala Ala Asp Arg Arg Phe			Arg Pro Pro Thr Asn Leu Arg			
	60		65	70		
agc gtg tgc ccc tgg gcg tac agg att			tcc tac gac cct gct cgc ttt	336		
Ser Val Ser Pro Trp Ala Tyr Arg Ile			Ser Tyr Asp Pro Ala Arg Phe			
	75		80	85		
ccg agg tac ctg ccc gaa gcc tac tgc			ctg tgc cga ggc tgc ctg acc	384		
Pro Arg Tyr Leu Pro Glu Ala Tyr Cys			Leu Cys Arg Gly Cys Leu Thr			
	90		95	100		
ggg ctc tac ggg gag gag gac ttc cgc			ttt cgc agc aca ccc gtc ttc	432		
Gly Leu Tyr Gly Glu Glu Asp Phe Arg			Phe Arg Ser Thr Pro Val Phe			
	105		110	115		120
tct cca gcc gtg gtg ctg ccg cgc aca			gcg gcc tgc gcg ggc ggc cgc	480		
Ser Pro Ala Val Val Leu Arg Arg Thr			Ala Ala Cys Ala Gly Gly Arg			
	125		130	135		
tct gtg tac gcc gaa cac tac atc acc			atc ccg gtg ggc tgc acc tgc	528		
Ser Val Tyr Ala Glu His Tyr Ile Thr			Ile Pro Val Gly Cys Thr Cys			
	140		145	150		
gtg ccc gag ccg gac aag tcc gcg gac			agt gcg aac tcc agc atg gac	576		
Val Pro Glu Pro Asp Lys Ser Ala Asp			Ser Ala Asn Ser Ser Met Asp			
	155		160	165		
aag ctg ctg ctg ggg ccc gcc gac agg			cct gcg ggg cgc tgatgccggg	625		
Lys Leu Leu Leu Gly Pro Ala Asp Arg			Pro Ala Gly Arg			
	170		175	180		
gactgcccgc catggcccag cttctgcat			gcatacaggtc ccctggccct gacaaaaccc	685		
accccatgat ccctggccgc tgccctaattt			ttccaaaagg acagctacat aagctttaaa	745		
tatatatttc aaagtagaca ctacatatct			acaactattt tgaatagtgg cagaaactat	805		
tttcatatta gtaatttaga gcaagcatgt			tggtttttaa cttctttgat atacaagcac	865		
atcacacaca tcccgttttc ctctagtagg			attcttgagt gcataattgt agtgctcaga	925		
tgaacttcct tctgctgcac tgtgccctgt			ccctgagtct ctctgtggc ccaagcttac	985		

taaggtgata atgagtgtctc cggatctggg cacctaaggt ctccaggtcc ctggagaggg 1045
 agggatgtgg gggggctagg aaccaagcgc ccctttgttc tttagcttat ggatggtctt 1105
 aactttataa agattaaagt ttttggtgtt attctttc 1143

<210> 12
 <211> 205
 <212> PRT
 <213> rodent

<400> 12
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 -5 -1 1 5
 Ala Arg Pro Arg Asp Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln
 10 15 20
 Leu Tyr Gly Arg Leu Ala Ala Gly Val Leu Ser Ala Phe His His Thr
 25 30 35 40
 Leu Gln Leu Gly Pro Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala
 45 50 55
 Gly Gly Arg Ala Ala Asp Arg Arg Phe Arg Pro Pro Thr Asn Leu Arg
 60 65 70
 Ser Val Ser Pro Trp Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Phe
 75 80 85
 Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr
 90 95 100
 Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Thr Pro Val Phe
 105 110 115 120
 Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala Cys Ala Gly Gly Arg
 125 130 135
 Ser Val Tyr Ala Glu His Tyr Ile Thr Ile Pro Val Gly Cys Thr Cys
 140 145 150
 Val Pro Glu Pro Asp Lys Ser Ala Asp Ser Ala Asn Ser Ser Met Asp
 155 160 165
 Lys Leu Leu Leu Gly Pro Ala Asp Arg Pro Ala Gly Arg
 170 175 180

<210> 13
 <211> 504
 <212> DNA
 <213> primate

<220>
 <221> CDS

<222> (19)..(501)

<220>

<221> mat_peptide

<222> (67)..(501)

<400> 13

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                    -15                      -10

atg gga acc cac acc tac agc cac tgg ccc agc tgc tgc ccc agc aaa 99
Met Gly Thr His Thr Tyr Ser His Trp Pro Ser Cys Cys Pro Ser Lys
-5                      -1 1                      5                      10

ggg cag gac acc tct gag gag ctg ctg agg tgg agc act gtg cct gtg 147
Gly Gln Asp Thr Ser Glu Glu Leu Arg Trp Ser Thr Val Pro Val
                      15                      20                      25

cct ccc cta gag cct gct agg ccc aac cgc cac cca gag tcc tgt agg 195
Pro Pro Leu Glu Pro Ala Arg Pro Asn Arg His Pro Glu Ser Cys Arg
                      30                      35                      40

gcc agt gaa gat gga ccc ctc aac agc agg gcc atc tcc ccc tgg aga 243
Ala Ser Glu Asp Gly Pro Leu Asn Ser Arg Ala Ile Ser Pro Trp Arg
                      45                      50                      55

tat gag ttg gac aga gac ttg aac cgg ctc ccc cag gac ctg tac cac 291
Tyr Glu Leu Asp Arg Asp Leu Asn Arg Leu Pro Gln Asp Leu Tyr His
60                      65                      70                      75

gcc cgt tgc ctg tgc ccg cac tgc gtc agc cta cag aca ggc tcc cac 339
Ala Arg Cys Leu Cys Pro His Cys Val Ser Leu Gln Thr Gly Ser His
                      80                      85                      90

atg gac ccc cgg ggc aac tcg gag ctg ctc tac cac aac cag act gtc 387
Met Asp Pro Arg Gly Asn Ser Glu Leu Leu Tyr His Asn Gln Thr Val
                      95                      100                      105

ttc tac cgg cgg cca tgc cat ggc gag aag ggc acc cac aag ggc tac 435
Phe Tyr Arg Arg Pro Cys His Gly Glu Lys Gly Thr His Lys Gly Tyr
110                      115                      120

tgc ctg gag cgc agg ctg tac cgt gtt tcc tta gct tgt gtg tgt gtg 483
Cys Leu Glu Arg Arg Leu Tyr Arg Val Ser Leu Ala Cys Val Cys Val
125                      130                      135

cgg ccc cgt gtg atg ggc tag 504
Arg Pro Arg Val Met Gly
140                      145

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<210> 14

<211> 161

<212> PRT

<213> primate

<400> 14

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Met Tyr Gln Val Val Ala Phe Leu Ala Met Val Met Gly Thr His Thr
-15                      -10                      -5                      -1

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Tyr Ser His Trp Pro Ser Cys Cys Pro Ser Lys Gly Gln Asp Thr Ser
 1 5 10 15
 Glu Glu Leu Leu Arg Trp Ser Thr Val Pro Val Pro Pro Leu Glu Pro
 20 25 30
 Ala Arg Pro Asn Arg His Pro Glu Ser Cys Arg Ala Ser Glu Asp Gly
 35 40 45
 Pro Leu Asn Ser Arg Ala Ile Ser Pro Trp Arg Tyr Glu Leu Asp Arg
 50 55 60
 Asp Leu Asn Arg Leu Pro Gln Asp Leu Tyr His Ala Arg Cys Leu Cys
 65 70 75 80
 Pro His Cys Val Ser Leu Gln Thr Gly Ser His Met Asp Pro Arg Gly
 85 90 95
 Asn Ser Glu Leu Leu Tyr His Asn Gln Thr Val Phe Tyr Arg Arg Pro
 100 105 110
 Cys His Gly Glu Lys Gly Thr His Lys Gly Tyr Cys Leu Glu Arg Arg
 115 120 125
 Leu Tyr Arg Val Ser Leu Ala Cys Val Cys Val Arg Pro Arg Val Met
 130 135 140
 Gly
 145

<210> 15
 <211> 620
 <212> DNA
 <213> rodent

<220>
 <221> CDS
 <222> (1)..(432)

<400> 15
 CGG CAC AGG CGG CAC AAA GCC CGG AGA GTG GCT GAA GTG GAG CTC TGC 48
 Arg His Arg Arg His Lys Ala Arg Arg Val Ala Glu Val Glu Leu Cys
 1 5 10 15
 ATC TGT ATC CCC CCC AGA GCC TCT GAG CCA CAC CCA CCA CGC AGA ATC 96
 Ile Cys Ile Pro Pro Arg Ala Ser Glu Pro His Pro Pro Arg Arg Ile
 20 25 30
 CTG CAG GGC CAG CAA GGA TGG CCT CTC AAC AGC AGG GCC ATC TCT CCT 144
 Leu Gln Gly Gln Gln Gly Trp Pro Leu Asn Ser Arg Ala Ile Ser Pro
 35 40 45
 TGG AGC TAT GAG TTG GAC AGG GAC TTG AAT CGG GTC CCC CAG GAC TGG 192
 Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp Trp
 50 55 60
 TAC CAC GCT CGA TGC CTG TGC CCA CAC TGC GTC ACG CTA CAG ACA GGC 240
 Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Thr Leu Gln Thr Gly
 65 70 75 80

TCC CAC ATG GAC CCG CTG GGC AAC TCC GTC CCA CTT TAC CAC AAC CAG 288
 Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn Gln
 85 90 95
 ACG GTC TTC TAC CGG CGG CCA TGC ATG GCG AGG AAG GTA CCC ATC GCC 336
 Thr Val Phe Tyr Arg Arg Pro Cys Met Ala Arg Lys Val Pro Ile Ala
 100 105 110
 GCT ACT GCT TGG AGC GCA GGT CTA CCG AGT CTC CTT GGC TTG TGT GTG 384
 Ala Thr Ala Trp Ser Ala Gly Leu Pro Ser Leu Leu Gly Leu Cys Val
 115 120 125
 TGT GCG GCC CCG GGT CAT GGC TTA GTC ATG CTC ACC ATC TGC CTG AGG 432
 Cys Ala Ala Pro Gly His Gly Leu Val Met Leu Thr Ile Cys Leu Arg
 130 135 140
 TGAATGCCGG GTGGGAGAGA GGGCCAGGTG TACATCACCT GCCAATGCCG GCCGGGTTC A 492
 AGCCTGCAAA GCCTACCTGA AGCAGCAGGT CCCGGGACAG GATGGAGACT TGGGAGAGAA 552
 TCTGACTTTT GCAC TTTT TGGAGCATTTTG GGAAGAGCAG GTTCGCTTGT GCTGTAGAGA 612
 TGCTGTTG 620

<210> 16
 <211> 144
 <212> PRT
 <213> rodent

<400> 16
 Arg His Arg Arg His Lys Ala Arg Arg Val Ala Glu Val Glu Leu Cys
 1 5 10 15
 Ile Cys Ile Pro Pro Arg Ala Ser Glu Pro His Pro Pro Arg Arg Ile
 20 25 30
 Leu Gln Gly Gln Gln Gly Trp Pro Leu Asn Ser Arg Ala Ile Ser Pro
 35 40 45
 Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp Trp
 50 55 60
 Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Thr Leu Gln Thr Gly
 65 70 75 80
 Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn Gln
 85 90 95
 Thr Val Phe Tyr Arg Arg Pro Cys Met Ala Arg Lys Val Pro Ile Ala
 100 105 110
 Ala Thr Ala Trp Ser Ala Gly Leu Pro Ser Leu Leu Gly Leu Cys Val
 115 120 125
 Cys Ala Ala Pro Gly His Gly Leu Val Met Leu Thr Ile Cys Leu Arg
 130 135 140

<210> 17
 <211> 985

<212> DNA
<213> rodent

<220>
<221> CDS
<222> (1)..(507)

<220>
<221> mat_peptide
<222> {49}...(507)

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<400> 17
atg tac cag gct gtt gca ttc ttg gca atg atc gtg gga acc cac acc 48
Met Tyr Gln Ala Val Ala Phe Leu Ala Met Ile Val Gly Thr His Thr
-15 -10 -5 -1

gtc agc ttg cgg atc cag gag ggc tgc agt cac ttg ccc agc tgc tgc 96
Val Ser Leu Arg Ile Gln Glu Gly Cys Ser His Leu Pro Ser Cys Cys
1 5 10 15

ccc agc aaa gag caa gaa ccc ccg gag gag tgg ctg aag tgg agc tct 144
Pro Ser Lys Glu Gln Glu Pro Pro Glu Glu Trp Leu Lys Trp Ser Ser
20 25 30

gca tct gtg tcc ccc cca gag cct ctg agc cac acc cac cac gca gaa 192
Ala Ser Val Ser Pro Pro Glu Pro Leu Ser His Thr His His Ala Glu
35 40 45

tcc tgc agg gcc agc aag gat ggc ccc ctc aac agc agg gcc atc tct 240
Ser Cys Arg Ala Ser Lys Asp Gly Pro Leu Asn Ser Arg Ala Ile Ser
50 55 60

cct tgg agc tat gag ttg gac agg gac ttg aat cgg gtc ccc cag gac 288
Pro Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp
65 70 75 80

ctg tac cac gct cga tgc ctg tgc cca cac tgc gtc agc cta cag aca 336
Leu Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Ser Leu Gln Thr
85 90 95

ggc tcc cac atg gac ccg ctg ggc aac tcc gtc cca ctt tac cac aac 384
Gly Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn
100 105 110

cag acg gtc ttc tac cgg cgg cca tgc cat ggt gag gaa ggt acc cat 432
Gln Thr Val Phe Tyr Arg Arg Pro Cys His Gly Glu Glu Gly Thr His
115 120 125

cgc cgc tac tgc ttg gag cgc agg ctc tac cga gtc tcc ttg gct tgt 480
Arg Arg Tyr Cys Leu Glu Arg Arg Leu Tyr Arg Val Ser Leu Ala Cys
130 135 140

gtg tgt gtg cgg ccc cgg gtc atg gct tagtcatgct caccacctgc 527
Val Cys Val Arg Pro Arg Val Met Ala
145 150

ctgaggctga tgcccggttg ggagagaggg ccagggtgac aatcaccttg ccaatgcggg 587

ccgggttcaa gccctccaaa gccctacctg aagcagcagg ctcccgggac aagatggagg 647

acttggggag aaactctgac ttttgcaact tttggaagca cttttgggaa ggagcaggtt 707

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ccgcttggtgc tgctagagga tgctgtgtg gcattttctac tcaggaacgg actccaaagg 767
 cctgctgacc ctggaagcca tactcctggc tcctttcccc tgaatcccc aactcctggc 827
 acaggcactt tctccacctc tcccccttg ccttttggtg tgtttggtt tgcatgcaa 887
 ctctgcgtgc agccaggtgt aattgccttg aaggatggtt ctgaggtgaa agctgttatc 947
 gaaagtgaag agatttatcc aaataaacat ctgtgttt 985

<210> 18
 <211> 169
 <212> PRT
 <213> rodent

<400> 18
 Met Tyr Gln Ala Val Ala Phe Leu Ala Met Ile Val Gly Thr His Thr
 -15 -10 -5 -1
 Val Ser Leu Arg Ile Gln Glu Gly Cys Ser His Leu Pro Ser Cys Cys
 1 5 10 15
 Pro Ser Lys Glu Gln Glu Pro Pro Glu Glu Trp Leu Lys Trp Ser Ser
 20 25 30
 Ala Ser Val Ser Pro Pro Glu Pro Leu Ser His Thr His His Ala Glu
 35 40 45
 Ser Cys Arg Ala Ser Lys Asp Gly Pro Leu Asn Ser Arg Ala Ile Ser
 50 55 60
 Pro Trp Ser Tyr Glu Leu Asp Arg Asp Leu Asn Arg Val Pro Gln Asp
 65 70 75 80
 Leu Tyr His Ala Arg Cys Leu Cys Pro His Cys Val Ser Leu Gln Thr
 85 90 95
 Gly Ser His Met Asp Pro Leu Gly Asn Ser Val Pro Leu Tyr His Asn
 100 105 110
 Gln Thr Val Phe Tyr Arg Arg Pro Cys His Gly Glu Glu Gly Thr His
 115 120 125
 Arg Arg Tyr Cys Leu Glu Arg Arg Leu Tyr Arg Val Ser Leu Ala Cys
 130 135 140
 Val Cys Val Arg Pro Arg Val Met Ala
 145 150

<210> 19
 <211> 521
 <212> DNA
 <213> primate
 <220>
 <221> misc_feature
 <222> (1)..(521)
 <223> note= "n may be a, c, g, or t".

```

<400> 19
gacacggatg aggaccgcta tccacagaag ctggccttcg ccgagtgccct gtgcagaggg 60
tgtatcgatg cacggacggg ccgcgagaca gctgcgctca actccgtgcg gctgctccag 120
agcctgctgg tgctgcgccg ccggccctgc tcccgcgacg gctcgggggt cccacacact 180
ggggcctttg ccttccacac cgagttcatc cacgtccccg tcggctgcac ctgcgtgctg 240
ccccgttcaa gtgtgaccgc caaggccgtg gggcccttag ntgacaccgt gtgctcccca 300
gagggaaccc tatttatggg aattatggtt ttatatgctt cccacatact tggggctggc 360
atcccngctg gagacagccc cctgtttctat tcagctatat ggggagaaga gtagactttc 420
agctaagtga aaagtgaac gtgctgactg tctgctgctg tctactnat gctagcccca 480
gtgttcactc tgagcctgtt aaatataggc ggttatgtac c 521

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<210> 20
<211> 521
<212> DNA
<213> primate

```

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<220>
<221> CDS
<222> (1)..(369)

```

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<220>
<221> misc feature
<222> (281)
<223> note= "nucleotides 281, 367, 437, 462, and 468 are
indicated c; each may alternatively be a, g, or t;
translated amino acid depends on genetic code"

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```

<400> 20
gac acg gat gag gac cgc tat cca cag aag ctg gcc ttc gcc gag tgc 48
Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu Cys
1 5 10 15

ctg tgc aga ggc tgt atc gat gca cgg acg ggc cgc gag aca gct gcg 96
Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala
20 25 30

ctc aac tcc gtg cgg ctg ctc cag agc ctg ctg gtg ctg cgc cgc cgg 144
Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg
35 40 45

ccc tgc tcc cgc gac ggc tcg ggg ctc ccc aca cct ggg gcc ttt gcc 192
Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala
50 55 60

ttc cac acc gag ttc atc cac gtc ccc gtc ggc tgc acc tgc gtg ctg 240
Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu
65 70 75 80

ccc cgt tca agt gtg acc gcc aag gcc gtg ggg ccc tta gct gac acc 288
Pro Arg Ser Ser Val Thr Ala Lys Ala Val Gly Pro Leu Ala Asp Thr
85 90 95

gtg tgc tcc cca gag gga ccc cta ttt atg gga att atg gta tta tat 336
Val Cys Ser Pro Glu Gly Pro Leu Phe Met Gly Ile Met Val Leu Tyr
100 105 110

gct tcc cac ata ctt ggg gct ggc atc ccg cgc tgagacagcc ccctgttcta 389
Ala Ser His Ile Leu Gly Ala Gly Ile Pro Arg
115 120

```

ttcagctata tggggagaag agtagacttt cagctaagtg aaaagtgcaa cgtgctgact 449
 gtctgctgtc gtcctactca tgctagcccg agtggtcact ctgagcctgt taaatatagg 509
 cggttatgta cc 521

<210> 21
 <211> 123
 <212> PRT
 <213> primate

<400> 21
 Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu Cys
 1 5 10 15
 Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala
 20 25 30
 Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg
 35 40 45
 Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala
 50 55 60
 Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu
 65 70 75 80
 Pro Arg Ser Ser Val Thr Ala Lys Ala Val Gly Pro Leu Ala Asp Thr
 85 90 95
 Val Cys Ser Pro Glu Gly Pro Leu Phe Met Gly Ile Met Val Leu Tyr
 100 105 110
 Ala Ser His Ile Leu Gly Ala Gly Ile Pro Arg
 115 120

<210> 22
 <211> 1107
 <212> DNA
 <213> primate

<220>
 <221> CDS
 <222> (115)..(705)
 <220>
 <221> mat_peptide
 <222> (166)..(705)

<400> 22
 gtgtggcctc aggtataaga ggggtgctg ccaggtgcat ggccaggtgc acctgtggga 60
 ttgccgccag gtgtgcaggc cgctccaagc ccagcctgcc ccgctgccgc cacc atg 117
 Met
 acg ctc ctc ccc ggc ctc ctg ttt ctg acc tgg ctg cac aca tgc ctg 165
 Thr Leu Leu Pro Gly Leu Leu Phe Leu Thr Trp Leu His Thr Cys Leu
 -15 -10 -5 -1

gcc cac cat gac ccc tcc ctc agg ggg cac ccc cac agt cac ggt acc 213
 Ala His His Asp Pro Ser Leu Arg Gly His Pro His Ser His Gly Thr
 1 5 10 15
 cca cac tgc tac tcg gct gag gaa ctg ccc ctc ggc cag gcc ccc cca 261
 Pro His Cys Tyr Ser Ala Glu Glu Leu Pro Leu Gly Gln Ala Pro Pro
 20 25 30
 cac ctg ctg gct cga ggt gcc aag tgg ggg cag gct ttg cct gta gcc 309
 His Leu Leu Ala Arg Gly Ala Lys Trp Gly Gln Ala Leu Pro Val Ala
 35 40 45
 ctg gtg tcc agc ctg gag gca gca agc cac agg ggg agg cac gag agg 357
 Leu Val Ser Ser Leu Glu Ala Ala Ser His Arg Gly Arg His Glu Arg
 50 55 60
 ccc tca gct acg acc cag tgc ccg gtg ctg cgg ccg gag gag gtg ttg 405
 Pro Ser Ala Thr Thr Gln Cys Pro Val Leu Arg Pro Glu Glu Val Leu
 65 70 75 80
 gag gca gac acc cac cag cgc tcc atc tca ccc tgg aga tac cgt gtg 453
 Glu Ala Asp Thr His Gln Arg Ser Ile Ser Pro Trp Arg Tyr Arg Val
 85 90 95
 gac acg gat gag gac cgc tat cca cag aag ctg gcc ttc gcc gag tgc 501
 Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu Cys
 100 105 110
 ctg tgc aga ggc tgt atc gat gca cgg acg ggc cgc gag aca gct gcg 549
 Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala Ala
 115 120 125
 ctc aac tcc gtg cgg ctg ctc cag agc ctg ctg gtg ctg cgc cgc cgg 597
 Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg Arg
 130 135 140
 ccc tgc tcc cgc gac ggc tcg ggg ctc ccc aca cct ggg gcc ttt gcc 645
 Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe Ala
 145 150 155 160
 ttc cac acc gag ttc atc cac gtc ccc gtc ggc tgc acc tgc gtg ctg 693
 Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val Leu
 165 170 175
 ccc cgt tca gtg tgaccgccga ggccgtgggg cccctagact ggacacgtgt 745
 Pro Arg Ser Val
 180
 gctccccaga gggcaccccc tatttatgtg tatttattgg tatttatatg cctcccccaa 805
 cactaccctt ggggtctggg cattccccgt gtctggagga cagcccccca ctgttctcct 865
 catctccagc ctcatgtgtt gggggtagaa ggagctcagc acctcttcca gcccttaaag 925
 ctgcagaaaa ggtgtcacac ggcgcctgt accttggttc cctgtcctgc tcccggcttc 985
 ccttacccta tcactggcct caggcccccg caggctgcct ctccccaacc tccctggaag 1045
 taccctgtt tcttaaaca tttttaagt gtacgtgtat tattaaactg atgaacacat 1105

cc

1107

<210> 23
<211> 197
<212> PRT
<213> primate

<400> 23
Met Thr Leu Leu Pro Gly Leu Leu Phe Leu Thr Trp Leu His Thr Cys
-15 -10 -5
Leu Ala His His Asp Pro Ser Leu Arg Gly His Pro His Ser His Gly
-1 1 5 10 15
Thr Pro His Cys Tyr Ser Ala Glu Glu Leu Pro Leu Gly Gln Ala Pro
20 25 30
Pro His Leu Leu Ala Arg Gly Ala Lys Trp Gly Gln Ala Leu Pro Val
35 40 45
Ala Leu Val Ser Ser Leu Glu Ala Ala Ser His Arg Gly Arg His Glu
50 55 60
Arg Pro Ser Ala Thr Thr Gln Cys Pro Val Leu Arg Pro Glu Glu Val
65 70 75
Leu Glu Ala Asp Thr His Gln Arg Ser Ile Ser Pro Trp Arg Tyr Arg
80 85 90 95
Val Asp Thr Asp Glu Asp Arg Tyr Pro Gln Lys Leu Ala Phe Ala Glu
100 105 110
Cys Leu Cys Arg Gly Cys Ile Asp Ala Arg Thr Gly Arg Glu Thr Ala
115 120 125
Ala Leu Asn Ser Val Arg Leu Leu Gln Ser Leu Leu Val Leu Arg Arg
130 135 140
Arg Pro Cys Ser Arg Asp Gly Ser Gly Leu Pro Thr Pro Gly Ala Phe
145 150 155
Ala Phe His Thr Glu Phe Ile His Val Pro Val Gly Cys Thr Cys Val
160 165 170 175
Leu Pro Arg Ser Val
180

<210> 24
<211> 403
<212> DNA
<213> primate

<220>
<221> misc_feature
<222> (1)..(403)
<223> note= "n may be a, c, g, or t"

<400> 24
gagaaagagc ttcctgcaca aagtaagcca ccagcgcaac atgacagtga agaccctgca 60

```

tggcccagcc atgggtcaagt acttgctgct gtcgatattg gggcttgcc ttcgtagtga 120
ggcggcagct cggaaaatcc ccaaagtagg acatactttt ttccaaaagc ctgagagttg 180
cccgctgtg ccaggaggta gtatgaagct tgacattggc atcatcaatg aaaaccagcg 240
cgtttccatg tcacgtaaca tcgagagccg ctccacctcc ccttgaatt acactgtcac 300
ttgggacccc aaccggtagc cctcgaagtt gtacaggccc aagtgtagga acttgggctg 360
tatcaatgct caaggaaagg aagacatctn catgaattcc gtc 403

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<210> 25
 <211> 403
 <212> DNA
 <213> primate

<220>
 <221> CDS
 <222> (71)..(403)

<220>
 <221> mat_peptide
 <222> (131)..(403)

<220>
 <221> misc_feature
 <222> (1)..(403)
 <223> note= "n may be a, c, g, or t; translated amino
 acid depends on genetic code"

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<400> 25
gagaaagagc ttcctgcaca aagtaagcca ccagcgcaac atgacagtga agaccctgca 60

tggcccagcc atg gtc aag tac ttg ctg ctg tcg ata ttg ggg ctt gcc 109
Met Val Lys Tyr Leu Leu Ser Ile Leu Gly Leu Ala
-20 -15 -10

ttt ctg agt gag gcg gca gct cgg aaa atc ccc aaa gta gga cat act 157
Phe Leu Ser Glu Ala Ala Arg Lys Ile Pro Lys Val Gly His Thr
-5 -1 1 5

ttt ttc caa aag cct gag agt tgc ccg cct gtg cca gga ggt agt atg 205
Phe Phe Gln Lys Pro Glu Ser Cys Pro Pro Val Pro Gly Gly Ser Met
10 15 20 25

aag ctt gac att ggc atc atc aat gaa aac cag cgc gtt tcc atg tca 253
Lys Leu Asp Ile Gly Ile Ile Asn Glu Asn Gln Arg Val Ser Met Ser
30 35 40

cgt aac atc gag agc cgc tcc acc tcc ccc tgg aat tac act gtc act 301
Arg Asn Ile Glu Ser Arg Ser Thr Ser Pro Trp Asn Tyr Thr Val Thr
45 50 55

tgg gac ccc aac cgg tac ccc tcg aag ttg tac agg ccc aag tgt agg 349
Trp Asp Pro Asn Arg Tyr Pro Ser Lys Leu Tyr Arg Pro Lys Cys Arg
60 65 70

aac ttg ggc tgt atc aat gct caa gga aag gaa gac atc tnc atg aat 397
Asn Leu Gly Cys Ile Asn Ala Gln Gly Lys Glu Asp Ile Xaa Met Asn
75 80 85

tcc gtc 403
Ser Val
90

```

<210> 26
 <211> 111
 <212> PRT
 <213> primate

<400> 26
 Met Val Lys Tyr Leu Leu Leu Ser Ile Leu Gly Leu Ala Phe Leu Ser
 -20 -15 -10 -5
 Glu Ala Ala Ala Arg Lys Ile Pro Lys Val Gly His Thr Phe Phe Gln
 -1 1 5 10
 Lys Pro Glu Ser Cys Pro Pro Val Pro Gly Gly Ser Met Lys Leu Asp
 15 20 25
 Ile Gly Ile Ile Asn Glu Asn Gln Arg Val Ser Met Ser Arg Asn Ile
 30 35 40
 Glu Ser Arg Ser Thr Ser Pro Trp Asn Tyr Thr Val Thr Trp Asp Pro
 45 50 55 60
 Asn Arg Tyr Pro Ser Lys Leu Tyr Arg Pro Lys Cys Arg Asn Leu Gly
 65 70 75
 Cys Ile Asn Ala Gln Gly Lys Glu Asp Ile Xaa Met Asn Ser Val
 80 85 90

<210> 27
 <211> 784
 <212> DNA
 <213> primate

<220>
 <221> CDS
 <222> (3)..(281)

<400> 27
 tc gtg ccg tat ctt ttt aaa aaa att att ctt cac ttt ttt gcc tcc 47
 Val Pro Tyr Leu Phe Lys Lys Ile Ile Leu His Phe Phe Ala Ser
 1 5 10 15
 tat tac ttg tta ggg aga ccc aat ggt agt ttt att cct tgg gga tac 95
 Tyr Tyr Leu Leu Gly Arg Pro Asn Gly Ser Phe Ile Pro Trp Gly Tyr
 20 25 30
 ata gta aat act tca tta aag tcg agt aca gaa ttt gat gaa aag tgt 143
 Ile Val Asn Thr Ser Leu Lys Ser Ser Thr Glu Phe Asp Glu Lys Cys
 35 40 45
 gga tgt gtg gga tgt act gcc gcc ttc aga agt cca cac act gcc tgg 191
 Gly Cys Val Gly Cys Thr Ala Ala Phe Arg Ser Pro His Thr Ala Trp
 50 55 60
 agg gag aga act gct gtt tat tca ctg att aag cat ttg ctg tgt acc 239
 Arg Glu Arg Thr Ala Val Tyr Ser Leu Ile Lys His Leu Leu Cys Thr
 65 70 75
 aac tac ttt tca tgt ctt atc tta att ctc ata aca gtc att 281

Asn Tyr Phe Ser Cys Leu Ile Leu Ile Leu Ile Thr Val Ile
80 85 90

tgatatttta aaaaacccca gaaatctgag aaagagataa agtgggttgc tcaagggttat 341
agaacagact accatgtggt gtatttcaga ttttaattca tgtttgtctg attttaagtt 401
ttgttcgctt gccagggtac cccacaaaaa tgccaggcag ggcattttca tgatgcactt 461
gagatacctg aaatgacagg gtagcatcac acctgagagg ggtaaaggat gggaacctac 521
cttccatggc cgctgcttgg cagtctcttg ctgcatgcta gcagagccac tgtatatgtg 581
ccgaggctct gagaattaac tgcttaaaga actgccttct ggaggggagaa gagcacaaga 641
tcacaattaa ccatatacac atcttactgt gcgaggtcac tgagcaatac aggagggatt 701
ttatacattt tagcaactat cttcaaaacc tgagctatag ttgtattctg ccccttcct 761
ctggggcaaaa gtgtaaaagt ttg 784

<210> 28
<211> 93
<212> PRT
<213> primate

<400> 28
Val Pro Tyr Leu Phe Lys Lys Ile Ile Leu His Phe Phe Ala Ser Tyr
1 5 10 15
Tyr Leu Leu Gly Arg Pro Asn Gly Ser Phe Ile Pro Trp Gly Tyr Ile
20 25 30
Val Asn Thr Ser Leu Lys Ser Ser Thr Glu Phe Asp Glu Lys Cys Gly
35 40 45
Cys Val Gly Cys Thr Ala Ala Phe Arg Ser Pro His Thr Ala Trp Arg
50 55 60
Glu Arg Thr Ala Val Tyr Ser Leu Ile Lys His Leu Leu Cys Thr Asn
65 70 75 80
Tyr Phe Ser Cys Leu Ile Leu Ile Leu Ile Thr Val Ile
85 90

<210> 29
<211> 460
<212> DNA
<213> primate

<220>
<221> CDS
<222> (1)..(189)

<400> 29
gtg act gta ttg tgg gga cag gaa gca caa att ccc atg tgg atc act 48
Val Thr Val Leu Trp Gly Gln Glu Ala Gln Ile Pro Met Trp Ile Thr
1 5 10 15

```

agg aga gat aat aag tgg ggt cat ttc acc cct tgg tcc cct gct tcc 96
Arg Arg Asp Asn Lys Trp Gly His Phe Thr Pro Trp Ser Pro Ala Ser
      20              25              30

aga ccc aaa gag gcc tac atg gca ttg tgc ttc ctt ctt agt tgt agg 144
Arg Pro Lys Glu Ala Tyr Met Ala Leu Cys Phe Leu Leu Ser Cys Arg
      35              40              45

agg tgt gag ata caa tca ttt gcc tct gac ttt gag ggt tgg tcc 189
Arg Cys Glu Ile Gln Ser Phe Ala Ser Asp Phe Glu Gly Trp Ser
      50              55              60

tagcatgccc ctgaccagta gcccttaaa tacttcattg atatggaagg tctctgaatc 249
ttcgtgggct taatctacca ctctctgaag ttcttatgtc tttcaaaggc ctctaaaatc 309
tctgccatgt cttgctcatc cagttgttag catgatgtca ttgatacagt ggacttttga 369
atctaagtgg ggagacactg gtaagtgacc aattacttca cctgtggtgt gcaagccaga 429
tcaggaagcc tctacctgca cgacaacaca t 460

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<210> 30
 <211> 63
 <212> PRT
 <213> primate

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<400> 30
Val Thr Val Leu Trp Gly Gln Glu Ala Gln Ile Pro Met Trp Ile Thr
  1              5              10              15

Arg Arg Asp Asn Lys Trp Gly His Phe Thr Pro Trp Ser Pro Ala Ser
      20              25              30

Arg Pro Lys Glu Ala Tyr Met Ala Leu Cys Phe Leu Leu Ser Cys Arg
      35              40              45

Arg Cys Glu Ile Gln Ser Phe Ala Ser Asp Phe Glu Gly Trp Ser
      50              55              60

```

<210> 31
 <211> 150
 <212> PRT
 <213> rodent

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<400> 31
Met Cys Leu Met Leu Leu Leu Leu Leu Asn Leu Glu Ala Thr Val Lys
  1              5              10              15

Ala Ala Val Leu Ile Pro Gln Ser Ser Val Cys Pro Asn Ala Glu Ala
      20              25              30

Asn Asn Phe Leu Gln Asn Val Lys Val Asn Leu Lys Val Ile Asn Ser
      35              40              45

Leu Ser Ser Lys Ala Ser Ser Arg Arg Pro Ser Asp Tyr Leu Asn Arg
      50              55              60

Ser Thr Ser Pro Trp Thr Leu Ser Arg Asn Glu Asp Pro Asp Arg Tyr

```

65 70 75 80
 Pro Ser Val Ile Trp Glu Ala Gln Cys Arg His Gln Arg Cys Val Asn
 85 90 95
 Ala Glu Gly Lys Leu Asp His His Met Asn Ser Val Leu Ile Gln Gln
 100 105 110
 Glu Ile Leu Val Leu Lys Arg Glu Pro Glu Lys Cys Pro Phe Thr Phe
 115 120 125
 Arg Val Glu Lys Met Leu Val Gly Val Gly Cys Thr Cys Val Ser Ser
 130 135 140
 Ile Val Arg His Ala Ser
 145 150

 <210> 32
 <211> 147
 <212> PRT
 <213> rodent

 <400> 32
 Met Leu Leu Leu Leu Leu Ser Leu Ala Ala Thr Val Lys Ala Ala Ala
 1 5 10 15
 Ile Ile Pro Gln Ser Ser Ala Cys Pro Asn Thr Glu Ala Lys Asp Phe
 20 25 30
 Leu Gln Asn Val Lys Val Asn Leu Lys Val Phe Asn Ser Leu Gly Ala
 35 40 45
 Lys Val Ser Ser Arg Arg Pro Ser Asp Tyr Leu Asn Arg Ser Thr Ser
 50 55 60
 Pro Trp Thr Leu His Arg Asn Glu Asp Pro Asp Arg Tyr Pro Ser Val
 65 70 75 80
 Ile Trp Glu Ala Gln Cys Arg His Gln Arg Cys Val Asn Ala Glu Gly
 85 90 95
 Lys Leu Asp His His Met Asn Ser Val Leu Ile Gln Gln Glu Ile Leu
 100 105 110
 Val Leu Lys Arg Glu Pro Glu Ser Cys Pro Phe Thr Phe Arg Val Glu
 115 120 125
 Lys Met Leu Val Gly Val Gly Cys Thr Cys Val Ala Ser Ile Val Arg
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 Gln Ala Ala
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 20 25 30
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 35 40 45
 Leu Asn Ile His Asn Arg Asn Thr Asn Thr Asn Pro Lys Arg Ser Ser
 50 55 60
 Asp Tyr Tyr Asn Arg Ser Thr Ser Pro Trp Asn Leu His Arg Asn Glu
 65 70 75 80
 Asp Pro Glu Arg Tyr Pro Ser Val Ile Trp Glu Ala Lys Cys Arg His
 85 90 95
 Leu Gly Cys Ile Asn Ala Asp Gly Asn Val Asp Tyr His Met Asn Ser
 100 105 110
 Val Pro Ile Gln Gln Glu Ile Leu Val Leu Arg Arg Glu Pro Pro His
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 Thr Cys Val Thr Pro Ile Val His His Val Ala
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 35 40 45
 Ile Arg Asn Trp Asn Thr Ser Ser Lys Arg Ala Ser Asp Tyr Tyr Asn
 50 55 60
 Arg Ser Thr Ser Pro Trp Thr Leu His Arg Asn Glu Asp Gln Asp Arg
 65 70 75 80
 Tyr Pro Ser Val Ile Trp Glu Ala Lys Cys Arg Tyr Leu Gly Cys Val
 85 90 95
 Asn Ala Asp Gly Asn Val Asp Tyr His Met Asn Ser Val Pro Ile Gln
 100 105 110
 Gln Glu Ile Leu Val Val Arg Lys Gly His Gln Pro Cys Pro Asn Ser
 115 120 125

